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MAURICE C. PINCOFFS

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## PARENTERAL SULFAPYRIDINE; THE INTRAVENOUS USE OF SODIUM SULFAPYRIDINE AND A REPORT OF CLINICAL AND LABORATORY OBSERVATIONS ON THE USE OF A GLUCOSE-SULFAPYRIDINE SOLUTION\*

By MAXWELL FINLAND, M.D., F.A.C.P., FRANCIS C. LOWELL, M.D.,  
WILLIAM C. SPRING, JR., M.D., and F. H. LASKEY TAYLOR, Ph.D.,  
*Boston, Massachusetts*

MARSHALL and Long<sup>1</sup> have recently reported observations on the intravenous use of the sodium salt of sulfapyridine<sup>2</sup> in patients in whom it is desirable to attain high concentrations of sulfapyridine in the blood rapidly and in patients in whom oral therapy results in inadequate concentrations or entails undue discomfort. Since occasions similar to the ones they outlined frequently arise, and since under such conditions the procedure may be of life-saving value, further reports of the use of this compound seem justified. While the clinical findings reported in this paper with respect to sodium sulfapyridine are largely confirmatory, additional data are added concerning both the efficacy of this compound and its toxicity. The main subject of this paper, however, concerns clinical and laboratory investigations of a glucose-sulfapyridine solution which was prepared in an effort to obtain effective materials suitable for both intravenous and subcutaneous injection. The findings are reported in order to emphasize the importance of clinical and laboratory assay rather than to offer a new effective remedy.

### THE USE OF SODIUM SULFAPYRIDINE INTRAVENOUSLY

A summary of the more relevant data in each of 21 patients who received one or more intravenous injections of this compound is shown in table 1. For the most part these patients were suffering from severe acute infections, and the injections were given as a preliminary to oral sulfa-

\*Received for publication October 12, 1939.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) Boston City Hospital; and the Department of Medicine, Harvard Medical School, Boston.

TABLE I  
Summary of Cases Treated with Sodium Sulfapyridine Intravenously

Sodium Sulfapyridine Intravenously													
Num- ber	Sex and Age	Diagnosis	Day of Disease	Amount (gm.)	Saline Diluent (c.c.)	Time for Injection (min.)	Blood Concentration			Reactions	Other Specific Treatment	Outcome	Remarks
							Time After Injection	Free	Total				
1	M 55	Meningitis (?)	?	3.2	600	60	2 minutes 3 hours	2.3 1.3	2.6 1.6	Restlessness increased during injection	S.P. 68 g. p.o. in 5 days	Recovered	Smear of spinal fluid: Gram + cocci. Cultures all yielded no growth. S.P. detected in urine 15 minutes after injection begun. Innumerable colonies in blood cul- ture before treatment; none after treatment.
2	F 74	Meningitis, Pn. XIX	77	5.0	1500	150	2 minutes	10.5	10.5	None	S.P. 26 g. + P.A.B.S. 12 g. p.o. in 3½ days	Died	Blood culture positive before in- jection; was negative before oral drug was resumed.
3	M 14	L. Pneum., Pn. I	4	5.0	500	25	2 minutes	9.5	10.6	Diarrhea, irritational	S.P. 20 g. p.o. (3 g. be- fore) in 3½ days	Crisis	Blood culture positive before treat- ment. Meningitis developed after 2½ days of oral therapy.
4	M 74	L. Pneum., Pn. XIV	28	5.0	500	60	15 minutes	9.1	9.8	None	S.P. 53 g. p.o. in 6 days	Died	Blood culture: <i>Staph. aureus</i> (twice). * 14 hours later, after 3 g. p.o.
5	M 49	B. Pneum., laryngi- tis, tracheotomy	9	5.0	1000	45	*	10.6	11.2	None	S.P. 10 g. p.o. in 3 days	Died	Pneumonia complicated nephritis with anasarca. Blood cultures positive.
6	F 18	B. Pneum., Pn. VIII	4	5.0	500	60	—	—	—	Chill 1 hour after in- jection; auricular fibrillation	Serum, 300,000 units; transfusions, 800 c.c. days	Died in 16 hours	Blood cultures negative * 21 hours later, after 1.5 g. p.o.
7	M 63	B. Pneum., Pn. V	7	5.0	300	30	*	5.0	8.1	Thrombosis both veins	S.P. 36 g. p.o. in 5½ days	Crisis	* 20 hours later, after 4 g. p.o.; vomiting at this time.
8	M 41	L. Pneum., <i>Str. hem.</i>	6	4.0	2000	120	—	—	—	Chill (?), convulsion, "collapse," fluttering respiration	S.P. 32 g. p.o. in 6 days	Lysis	Injection interrupted because of reaction. Some extravasation with marked local reaction.
9	M 57	L. Pneum., Pn. III	7 5	4.0 ±2.5	2000 250	120 25	—	10.6	11.0	—	None	Died in 2 hours	Blood culture negative.
10	M 42	L. Pneum., Pn. III	5	4.0	80	15	*	6.2	8.3	None	S.P. 6 g. in 30 hours	Lysis	Severe delirium tremens on second day of treatment. Negative blood cultures.

Abbreviations: M = male; F = female; L. Pneum. = lobar pneumonia; B. Pneum. = bronchopneumonia; Pn. = pneumococcus (type is indicated by Roman numeral); S.P. = sulfapyridine; P.A.B.S. = sulfanilamide; p.o. = by mouth.  
Cases 19, 20, and 21 were subjects of a more detailed study to be reported elsewhere.

TABLE I—Continued

## Sodium Sulfapyridine Intravenously

Sodium Sulfapyridine

Num- ber	Sex and Age	*Diagnosis	Day of Disease	Amount (gm.)	Saline Diluent (c.c.)	Time for Injection (min.)	Blood Concentration			Reactions	Other Specific Treatment	Outcome	Remarks
							Time After Injection	Milligrams per 100 c.c.					
								Free	Total				
11	M 70	L. Pneum., Pn. III Meningitis	? 4h*	4.0 4.0	100 100	15 10	2 hours Before 10 minutes 1 hour† 4 hours 2 minutes	10.0 7.7 19.8 17.3 14.9 11.7	10.4 8.7 20.5 18.0 17.8 12.4	Vomiting, hiccup Pulmonary edema, 3 hours after this in- jection Restlessness increased, "collapse" Dizziness	None	Died 12 hours after first injection	* 4 hours after the first injection. † Spinal fluid concentration at this time 5.7 and 6.7 mg. per 100 c.c. free and total, respectively. Blood cultures positive before and after treatment. Blood cultures positive for 10 days. Rib resection.
12	F 76	L. Pneum., Pn. IV	?	4.0	1000	150	—	—	—	—	None	Died in 6 hours	Blood cultures positive before and after treatment. Blood cultures positive for 10 days. Rib resection.
13	F 52	L. Pneum., Pn. III Empyema	15	2.0	200	30	*	—	—	—	S.P. 114 g. p.o. 12 days before and 7 days after S.P. 4 g. p.o.	Recovered	Blood cultures positive before on admission; negative before sulfapyridine injection. * Level 16 hours later, after S.P. 3 g. p.o. Blood culture positive before sulfapyridine injection. * Level at time nausea began.
14	f 35	L. Pneum., Pn. I	8	4.0	80	20	*	5.0	8.7	None	S.P. 36 g. p.o. in 6 days begun 7 hours later S.P. 3 g. p.o. begun 2 hours later	Unim- proved	Concentration in spinal fluid 2 hours later = 3.7 free and 4.0 total; in stomach contents at this time = 33.2/33.2 mg. per 100 c.c. (before oral dose). * Hours after first injection. Pelvic abscess drained, multiple incisions with drainage of ab- dominal wall. Blood culture re- peatedly positive for <i>S. an.</i> after P.A.B.S. and before intravenous therapy, sterile after S.P. treat- ment.
15	M 22	Pulm. Tuberculosis B. Pneum. (?)	?	5.0	500	60	2 minutes 7 hours 5 minutes	3.7 8.3 3.7 9.7	3.8 8.6 5.6 10.4	Nausea after first 250 c.c. given in 10 min- utes None	P.A.B.S., 13 g. p.o. for first 3 days S.P. 40 g. p.o. in 5½ days, begun 24 hours after last injection	Died in 10 hours	
16	M 54	Meningitis, Pn. VII Alcoholism	?	5.0	500	90	30 minutes Before 2 minutes 2 hours Before 2 minutes Before 2 minutes	9.9 7.4 18.2 14.6 12.8 15.5 11.7 18.4	11.8 8.9 18.9 16.3 17.4 19.0 13.3 20.8	None	Recovered		
17	M 27	Peritonitis and post- operative wound sepsis, <i>Staph. au- reus</i>	7 5h* 11h* 24h* 31h* 36h* 55h*	5.0 5.0 2.5 5.0 2.5 2.5 2.5	500 500 250 500 250 250 250	26 45 45 30 30 30 30	Before 2 minutes 2 hours Before 2 minutes Before 2 minutes Before 20 hours	13.2 18.3 16.0 6.4 15.1 20.0 17.8 8.3					

TABLE I—Continued

Sodium Sulfapyridine Intravenously										Outcome	Remarks		
Num- ber	Sex and Age	Diagnosis	Day of Disease	Amount (gm.)	Saline Diluent (c.c.)	Time for Injection (min.)	Blood Concentration					Reactions	
							Time After End of Injection	Free	Total				
18	M 42	L. Pneum., Pn. I	2	5.0	500	50	10 minutes†	7.7	7.7	Vomited after 10 min- utes (150 c.c. in- jected)—continued for several hours	Serum 100,000 units given 29 hours after first dose because of failure to show any response	Crisis 5 hours after serum	* Hours after first injection. † Af- ter beginning of injection when patient vomited—vomitus at end of injection had 8.9 mg. per 100 c.c. free and total sulfapyridine. Vomitus before second injection had 16.3 and 17.4 mg. per 100 c.c. free and total, respectively. Total of 2.67 g. recovered from urine in 30 hours. All blood cultures negative. * After beginning of injection (af- ter 250 c.c.). Urine voided 30 minutes after be- ginning of injection had 33.4 and 36.4 mg. per 100 c.c. of free and total S.P., respectively. * After beginning of injection (af- ter 250 c.c.). Urine voided at this time had 4.7 and 6.3 mg. per 100 c.c. of free and total S.P., respectively. * After beginning of injection (af- ter 250 c.c.). Urine voided at this time had 9.0 and 10.0 mg. per 100 c.c. free and total S.P., respectively.
							2 minutes	9.9	9.9				
							2 hours	7.9	7.9				
							Before	7.5	7.5				
							2 minutes	17.4	17.4				
19	M 26	Gonococcal Arthri- tis	?	4.75	500	60	30 minutes*	7.7	7.7	Nausea at end of in- jection, lasted 6 hours	Misc. None for 3 days before or after this injection	Partly improved	
							2 minutes	9.9	9.9				
							5 hours	7.7	8.0				
							24 hours	3.5	3.7				
20	M 43	Arthritis, ? Gono- coccal	?	4.75	500	60	30 minutes*	4.4	5.3	Anorexia, nausea and malaise for 4 hours	Misc. None for 3 days before or after this injection	Improved	
							2 minutes	9.5	10.3				
							5 hours	5.0	7.4				
							11 hours	2.9	5.4				
							24 hours	trace	3.2				
21	M 62	Parotid abscess, after erysipelas	?	4.75	500	60	30 minutes*	5.1	5.9	Dizziness for 1 hour after injection	Misc. None for 3 days before or after injection	Improved	
							2 minutes	9.8	11.1				
							5 hours	5.7	7.6				
							11 hours	3.2	5.3				
							24 hours	trace	2.0				

pyridine therapy. In two patients the injections were followed by specific serum therapy. The last three patients listed were not severely ill. They were the subjects of comparative studies on sulfapyridine and related compounds given by various routes.<sup>3</sup>

Sterile physiological salt solution was used as the diluent in every instance. The amounts of the drug in each injection varied from 2.5 to 5.0 grams. This was given in from 80 to 2000 c.c. of saline, or in concentrations ranging from 0.2 to 5 per cent. For the most part a 1 per cent solution was used, the larger volumes being reserved for dehydrated patients. When the drug was given in a volume of 100 c.c. or less, it was injected from a syringe in 10 to 20 minutes. Larger volumes were given by a slow drip, taking from one-half to two and one-half hours for the injection. One of the patients received seven injections, three were given two, and the others a single injection.

The maximum concentrations, attained a few minutes after the end of the initial intravenous injections of 4 or 5 grams of sodium sulfapyridine, ranged from 8.6 to 12.4 mg. per 100 c.c., of which from 0 to 17 per cent was determined as "combined" (acetylated) and the rest as free sulfapyridine.<sup>4</sup> In most of the subjects the concentration was about 10 mg. per 100 c.c. with about 7 per cent acetylated. The percentage of drug circulating as acetylated sulfapyridine after a single injection gradually increased as the total concentration dropped, but levels as high as 5 mg. per cent were usually still present 12 hours after the injection, and 50 per cent or more of this was "free" sulfapyridine. A more detailed account of the fate of the injected material in the last three subjects is given elsewhere.<sup>3</sup>

The drug was detected in the urine within 15 minutes after the beginning of an injection, and concentrations as high as 36 mg. per 100 c.c. were found in the urine after 30 minutes when only 2.5 grams had been injected with 250 c.c. of saline. The concentrations of the drug in the spinal fluid one hour after an injection in Case 11 and two hours after the injection in Case 16 were one-third and one-half of the corresponding blood concentrations, suggesting that the equilibrium between blood and spinal fluid is not reached very rapidly.

The stomach contents were studied in two patients during and after injection. In Case 16, a stomach tube was introduced for the purpose of further drug administration two hours after the intravenous injection, just after the lumbar puncture was completed. A small amount of the stomach content, withdrawn for analysis before any further drug was given, contained free sulfapyridine in a concentration of 33.2 mg. per 100 c.c. One patient (Number 18) began to vomit 10 minutes after the beginning of an injection. The concentration of drug in blood taken at this time from the opposite antecubital vein was 7.7 mg. per cent. At the end of the injection, the concentration of the drug in the blood was 9.9 mg. per cent and in the vomitus it was 8.9 mg. per cent. Five hours later the patient was still vomiting and the material brought up contained 17.4 mg. of sulfapyridine per 100 c.c., of



which 16.3 mg. were in the free form. At this time the level in the blood was 7.5 mg. These findings suggest that when sodium sulfapyridine is injected intravenously it is excreted rapidly into the stomach and may be concentrated there. Coupled with the fact that many patients receiving sulfapyridine orally began to vomit within a few minutes after the first dose, these observations would indicate that local gastric irritation may be an important contributing factor in the nausea and vomiting irrespective of any possible central effect of the drug.

As in Marshall and Long's cases, nausea with or without vomiting was the most frequent toxic effect observed. In our cases, this usually began during the course of the injection and lasted for several hours. In one patient the vomiting was associated with diarrhea and the patient became irrational and excited for a few hours. The vomiting, but not the mental symptoms, reappeared late when oral therapy was started. A second patient began to hiccup at the same time and this symptom continued until three hours after a second injection when he developed increasing pulmonary edema. At this time the blood level was 17.8 mg. per cent of which 14.8 mg. were "free" sulfapyridine.

One patient (Number 7) had a moderately severe chill which began an hour after the injection and lasted 15 minutes, during which time his pulse rate rose from 100 to 160 per minute and he developed auricular fibrillation. His rhythm reverted rapidly to normal after digitalization. Two patients complained of dizziness which began toward the end of the injection and lasted for about an hour. In another patient restlessness, which was present before the injection, increased during and after the administration of the drug, and this was soon followed by "circulatory collapse." Thrombosis of the veins into which the drug was injected occurred in two instances: In one (Case 8) both antecubital veins were involved and no other intravenous injections had been given; in the other (Case 17) a number of veins became thrombosed, but these had been used for various forms of intravenous medication, including the sodium sulfapyridine.

In Case 9, a reaction to the drug may have been the immediate cause of death. This was a patient with incipient delirium tremens who was apparently quiet when the injection was begun. After about 25 minutes, when approximately one-half of the material had been injected, he exhibited some generalized muscular activity and appeared to be having a chill. Before the needle was withdrawn a small amount of the solution had extravasated into the subcutaneous tissues. The patient soon had definite tonic and clonic convulsions, after which his skin became cold, ashen gray in color and moist. His respiration became irregular and fluttering in character, he became comatose and died within two hours after the beginning of the injection. In the interim, the tissues around the extravasated material became red, then markedly edematous and almost fluctuant.

In nine of the patients, including the one who received seven injections, there were no untoward reactions of any sort.

The therapeutic effect of the drug is difficult to assess in a group of such severe cases, particularly since other therapy was used in most of the patients. The four patients with pneumococcic meningitis all died. None of them received serum. Two died within 12 hours and the others after three or more days of oral sulfapyridine therapy. One of the latter (Case 4) was being treated for pneumonia and had clear spinal fluid two and one-half days after sulfapyridine therapy was begun. His blood culture showed 300 pneumococcus colonies per c.c. before the intravenous injection, and he had received 30 grams of sulfapyridine at the time when the diagnosis of meningitis was established. One patient, who may have had meningitis, recovered. His spinal fluid on admission to the hospital was turbid and showed numerous polymorphonuclear leukocytes; rare gram-positive cocci were seen in a smear of the sediment. However, cultures of this fresh fluid and of those obtained subsequently all yielded no growth.

Nine of the patients, excluding one with meningitis, had pneumococcic pneumonia. The blood culture was positive in five, of whom three died within 18 hours of the injection. One of the latter had severe glomerular nephritis and was also given specific serum. The only death among the four patients with sterile blood cultures was in the alcoholic Type III patient who had the convulsion during the injection.

Three cases are of special interest:

—Case 18. A 42 year old man had Type I pneumococcus pneumonia and negative blood cultures. He received 10 grams of sodium sulfapyridine in two doses five hours apart. High concentrations were maintained for 29 hours without any appreciable effect on the course of the pulmonary infection. Crisis occurred five hours after the administration of 100,000 units of Type I antipneumococcic serum.

Case 8. A 41 year old man with lobar pneumonia had negative blood cultures, and hemolytic streptococci were obtained in almost pure culture from all the sputum specimens examined. He received two doses of four grams of sodium sulfapyridine intravenously 18 hours apart. Oral sulfapyridine therapy was begun eight hours after the second injection. He made an uneventful recovery except for thrombosis of his antecubital veins.

Case 17. A 27 year old man developed wound sepsis and peritonitis following an elective cholecystectomy. Blood cultures on two occasions during sulfanilamide therapy were positive for *Staphylococcus aureus*, prior to the first intravenous injection of sodium sulfapyridine. He was given seven injections of the latter drug over a period of two and one-half days, and then was given sulfapyridine by mouth. He was on Wangenstein drainage before and during the intravenous therapy because of persistent vomiting. Several abscesses of the abdominal wall and a large pelvic abscess were drained after several days, and the patient then made a slow but steady and uneventful recovery. It was felt that the institution of intravenous sodium sulfapyridine definitely marked the turning point in this patient who was failing rapidly and in whom, because of severe vomiting, effective oral therapy was impossible.

In another patient (Number 5) with *Staphylococcus aureus* bacteremia, associated with laryngo-tracheobronchitis and pneumonia, there was no effect from the drug. Tracheotomy had been done, and later additional oral therapy was given, but the patient died.

The observations on the clinical use of sodium sulfapyridine intraven-

ously may be summarized briefly. The drug was usually given slowly in four or five gram doses diluted to 1 per cent with physiological salt solution. High concentrations, usually 10 mg. per 100 c.c., were obtained rapidly in the blood, and these dropped rather slowly so that effective levels were still present six and sometimes 12 hours after a single injection. Acetylation began early and increased steadily. The drug appeared rapidly in the urine. In the spinal fluids, the concentration of the drug up to four hours after an injection was only one-half or less of the simultaneous blood level. The drug appeared rapidly in the stomach contents (withdrawn or vomited) and was found there in higher concentrations than in the blood. Reactions from the injections were usually of minor importance considering the severity of the cases treated. However, in one patient convulsions occurred during the injection and were rapidly followed by collapse, irregular respirations and death, and in a second the injections may have contributed to the early onset of pulmonary edema. The therapeutic value of the drug is difficult to assay because the number of cases is small and because additional therapy was given in most of the patients who were severely ill. In one patient with severe *Staphylococcus aureus* sepsis, the repeated intravenous injections of sodium sulfapyridine were probably life-saving.

#### GLUCOSE-SULFAPYRIDINE SOLUTION

Although it was found possible to maintain effective levels in some cases with two intravenous injections daily of sodium sulfapyridine, this material presented numerous undesirable features. The alkalinity of the solution offered the possibility of a sclerosing effect upon veins and of severe local necrosis resulting from accidental extravasation into the subcutaneous tissues. There was also the possibility of more than usual renal irritation<sup>5, 6, 7</sup> and of cerebral stimulation when large amounts of this material are rapidly introduced into the circulation. These considerations suggested the desirability of having the drug in a soluble non-irritative form that could be given subcutaneously in the necessary amounts with a convenient quantity of fluid. This would offer somewhat slower absorption, but, with adequate fluids, the drug could, if necessary, be mobilized more rapidly, thus overcoming Long's<sup>8</sup> objection to the oily suspensions suggested by Whitby.<sup>9</sup> The intramuscular injections of the sodium salt, especially where repeated large doses are necessary, did not seem desirable, although Gaisford<sup>10</sup> has used it by this route in 33 $\frac{1}{3}$  per cent solution, apparently without severe side effects.

The low solubility of sulfapyridine, which occasioned the introduction of the sodium salt, also led others to seek various methods of obtaining a stable solution of the drug in concentrations and in forms which are convenient for therapeutic purposes. Blake<sup>11</sup> succeeded in getting two grams of sulfapyridine into solution in a liter of fluid consisting of equal parts of 5 per cent glucose (in distilled water) and physiological saline which had been brought to a boil. This mixture then contained 0.2 per cent sulfapyridine which re-

mained in solution at room temperature for four days. He gave this solution intravenously, subcutaneously, and intrathecally, and was able to maintain high concentrations of sulfapyridine in the blood over considerable periods by such parenteral administration. We wished to obtain more concentrated solutions so that smaller volumes of fluid would suffice for parenteral use. It was found possible, by using more concentrated solutions of dextrose, to dissolve considerably larger amounts of sulfapyridine, but boiling became necessary to bring this about. The preparation of such solutions was then undertaken in the Research Division of the Lederle Laboratories, where it was found possible to dissolve upwards of 25 per cent sulfapyridine in 50 per cent dextrose. Solutions containing about 10 per cent sulfapyridine and 50 per cent dextrose in sterile ampoules were chosen, and these were supplied to us for clinical and laboratory studies. In the course of preparation and sterilization, these solutions assumed a slight golden brown color. These preparations were also supplied to Dr. Norman Plummer at Bellevue Hospital for independent studies.

*Clinical Observations.* The relevant data in 17 patients who received this solution by various routes are given in table 2. For the most part the solution was diluted 10 fold in physiological saline, so that the final concentration was 2 per cent sulfapyridine and 5 per cent glucose. The intravenous doses were usually injected in from 30 to 60 minutes, and the subcutaneous doses in one to three hours. One patient was given the original solution undiluted intravenously, and two others took it in this form by mouth. Each parenteral injection contained 50 c.c. of the original solution (equivalent to about five grams of sulfapyridine), except in some instances where the second or later doses contained only 25 c.c., or the equivalent of 2.5 grams of sulfapyridine.

The concentrations were determined by Marshall and Litchfield's method for sulfapyridine<sup>4</sup> just as in the previous cases. The significance of "free" (unconjugated) and "total" sulfapyridine as determined by this method in the present cases will be referred to below. After the intravenous injections of comparable amounts of glucose-sulfapyridine solution, the concentrations attained in the blood were appreciably higher than after comparable injections of sodium sulfapyridine. Within a few minutes after the injection of glucose solution containing five grams of sulfapyridine, the concentration in the blood determined as "total" sulfapyridine varied from 10.8 to 20.0 mg. per 100 c.c., of which from 6.6 to 100 per cent was determined as "unconjugated" sulfapyridine by the method used. These levels declined rapidly to one-half or less of the maximum concentration in two hours and to less than one-third in six hours. Only traces of drug were found in the blood after 12 hours. The maximum concentrations after single subcutaneous doses were attained from one to six hours after the injections and ranged from 3.6 to 6.6 mg. per 100 c.c., of which from 71 to 94 per cent was determined as free unconjugated sulfapyridine. The maximum concentrations from oral administration were attained 12 to 24 or more hours after ingestion, and

TABLE II  
Summary of Relevant Data Concerning Patients Who Received Sulfapyridine-Dextrose Solution

Sulfapyridine Dextrose Administration															
Num- ber	Sex and Age	Diagnosis	Day of Disease	S.P.—50% Glucose Solution (c.c.)	S.P. Content (gm.)	Total Volume (with Saline Diluent) (c.c.)	Route	Time for Adminis- tration (minutes)	Sulfapyridine Concen- tration in Blood			Reactions	Other Specific Treatment	Outcome	Remarks
									Time After Administra- tion Ended	Free	Total				
1	M 17	L. Pneum., Pn. XXIII Sterile pleural effusion	3	20 20 10	2.0 2.0 1.0	0 0 0	p.o. p.o. p.o.	— — —	2 hours 2 hours 12 hours	1.9 2.4 3.0	1.9 2.4 3.7	Vomited before and after	None	Crisis same day	3 doses given 2 hours apart.
2	M 26	Upper respiratory infection	1	20 20 10	2.0 2.0 1.0	0 0 0	p.o. p.o. p.o.	— — —	2 hours 4 hours 4 hours 14 hours 14 hours	1.1 1.4 1.7 2.2 4.0	1.1 1.4 1.7 2.2 4.5	Nausea 6 hours after last dose	None	Afebrile 1 hour after second dose	Doses 2 and 4 hours apart, respectively.
3	M 34	L. Pneum., Pn. VIII	2	50	5.0	400	i.v.	60	1 hour	10.3	10.3	None	None	Lysis after 10 hours	—
4	M 21	L. Pneum., Pn. V	4	50	5.0	500	i.v.	30	Before* 5 minutes 2 hours 11 hours 24 hours 5 minutes 1 hour 7 hours 14 hours 2 hours 8 hours	1.8 1.2 5.2 1.4 1.3 2.1 3.6 2.7 3.3 4.7 2.3	1.8 1.2 5.2 1.4 1.3 2.1 3.6 2.7 3.3 4.7 2.3	None	P.A.B.S., 4 g. p.o., 4 days previously S.P., 11 g. p.o. in 2 days begun after 36 hours None	Crisis, 30 hours after oral S.P.	* Sulfanilamide levels.
5	F 74	B. Pneum., Pn. IV	6	50	5.0	500	s.c.	120	1 hour 5 minutes 24 hours 5 minutes 1 hour 7 hours 14 hours 2 hours 8 hours	2.1 2.1 2.7 3.6 4.7 2.3	2.1 2.1 2.7 3.6 4.7 2.3	None	None	Lysis in 10-18 hours	Improving before treat- ment.
6	F 52	L. Pneum., Pn. III Empyema	17	50	5.0	0	i.v.	30	14 hours 2 hours 8 hours	1.3 4.7 2.3	1.3 4.7 2.3	"Chilly" 5 min- utes after injec- tion begun, no rise in tempera- ture	S.P. 44 g. p.o. before, 70 g. after this in- jection	Convales- cing	No S.P. for 3 days before and 9 hours after this injec- tion. Blood culture posi- tive before and after this injection.
7	M 24	L. Pneum., Pn. XIV	3	50	5.0	500	s.c.	60	5 minutes 1 hour 3 hours	3.7 4.6 2.3	3.7 4.6 2.3	Nausea 3 hours later	S.P. 13 g. p.o. in 2 days. Begun 24 hours after last s.c. dose	Crisis 2 hours after first oral dose	S.c. doses given 12 hours apart. Marked improve- ment after last injection.
			3½	25	2.5	300	s.c.	45	Before 3½ hours	2.4 2.7	2.4 2.7	None			
			4	25	2.5	300	s.c.	60	Before 3½ hours	2.2	2.2	None			

Abbreviations: M = male; F = female; L. Pneum. = lobar pneumonia; B. Pneum. = bronchopneumonia; Pn. = pneumococcus (type is indicated by Roman numeral); S.P. = sulfapyridine; P.A.B.S. = sulfanilamide; p.o. = by mouth; i.v. = intravenous; s.c. = subcutaneous; concentration + = trace.

TABLE II—Continued

Sulfapyridine Dextrose Administration												Outcome	Remarks	
Num- ber	Sex and Age	Diagnosis	Day of Disease	S.P.—50% Glucose Solution (c.c.)	S.P. Content (gm.)	Total Volume (with Saline Diluent) (c.c.)	Route	Time for Adminis- tration (minutes)	Sulfapyridine Concen- tration in Blood					Reactions
									Time After Administra- tion Ended	Free	Total			
8	M 67	B. Pneum., Pn. VII	5	50	5.0	500	s.c.	100	5 minutes 2 hours 6 hours 10½ hours	2.3 4.4 4.9 3.4	2.5 5.4 5.8 4.8	Fluid absorbed slowly. Tissues swollen for 4 hours	Lysis 3 days later	Chill 5 hours after s.c. dose. Process in lung extended.
9	M 18	L. Pneum., Pn. III Empyema	6	50	5.0	500	s.c.	180	5 minutes 3 hours* 8 hours	3.4 2.6 +	4.2 3.3 1.6	None	Lysis 3 days later	* Level in pleural exudate at this time = 1.8 (free and total). Closed tho- racotomy. * Tap water instead of sa- line.
10	M 18	B. Pneum., Pn. XIII, Pn. XXVIII and Strep. hem.	?	50	5.0	500*	p.o.	—	1 hour 2 hours 3 hours 8 hours	0 +	1.5 2.2 2.9	None	Lysis 2 days later	* 2 doses i.v. 5 hours apart, then repeated 2 days later.
11	M 50	Bronchiectasis, ? B. Pneum., Pn. VI	?	50	5.0	500	i.v.	30	2 minutes 2 hours Before*	11.8 4.1 2.3	15.4 5.6 3.1	Chill for 15 min- utes None	Improved and relapsed	
			+12	50	5.0	500	i.v.	30	2 minutes 5½ hours 2 minutes 2 hours	15.8 2.7 9.8 6.0	20.4 3.8 10.0 6.6	None None		
				50	5.0	500	i.v.	30	Before* 2 hours 4½ hours 5 minutes 6 hours	16.7 7.4 4.3 13.3 3.5	16.7 8.0 4.8 14.3 4.2	None None	Lysis 2 days later	Fever for 2 weeks.
12	M 44	L. Pneum., Strep. hem. (?)	5	50	4.75	500	i.v.	30						



varied from 2.9 to 5.6 mg. per 100 c.c., of which from 55 to 89 per cent was in the "free" form. In one patient with empyema the pleural fluid obtained three hours after a subcutaneous injection had a concentration of 1.8 mg. of drug (free and total) and the blood at this time had 3.3 mg., of which 2.6 mg. were determined as free sulfapyridine.

Untoward reactions from this solution were considerably less than after the sodium salt. There were no venous thromboses noted and there was no discomfort whatever from the subcutaneous injections. One patient vomited both before and after taking the solution by mouth. Three other patients had nausea, two after oral and one after subcutaneous doses, and in each instance this symptom began two hours or more after the drug was given.

The cases treated with the glucose sulfapyridine solution were considerably milder than those treated with the sodium salt. One patient (Number 2) had symptoms suggesting the onset of pneumonia and had a critical drop in temperature and subsidence of symptoms within a few hours after taking the solution by mouth, but neither physical findings nor roentgen-ray examinations showed any pulmonary involvement. In three patients with pneumonia (Numbers 1, 3, and 5) the drug appeared to be efficacious, since there was rapid recovery within a few hours after its administration and no other specific therapy was used. Each of these patients had received the drug by a different route. In most of the other patients with pneumonia, the subsequent administration of sulfapyridine orally made a proper estimation of the value of the glucose solution difficult. However, none of the cases with typical pneumonia showed definite improvement before the oral sulfapyridine therapy was begun, although the equivalent of from 5 to 15 grams had already been given parenterally in the form of the glucose solution, and all recovered rapidly after receiving tablets of sulfapyridine orally. These findings suggested that the effect of the material that we were giving in glucose solution was not very striking and was certainly not equivalent to the effect to be expected from corresponding amounts of sulfapyridine or of its sodium salt.

#### CHEMICAL AND BACTERIOLOGICAL INVESTIGATIONS

Detailed comparative studies were undertaken in each of three subjects to determine the blood concentrations and the urinary excretion of single comparable doses of the glucose-sulfapyridine solution and sulfanilamide given orally, subcutaneously and intravenously, of sodium sulfapyridine given intravenously, and of sulfapyridine given orally. Studies were also made to determine the bactericidal action of these substances when added *in vitro* to cultures or to human blood, and similar studies were carried out with the blood of patients after the administration of these substances by various routes. The results are reported in detail elsewhere.<sup>3,12</sup> Certain of the observations bearing on the clinical findings presented may be summarized briefly.



Following the intravenous injection of a single dose of glucose-sulfapyridine the concentration of sulfapyridine attained in the blood is considerably greater than after the intravenous injection of the same amount of sodium sulfapyridine. The blood concentrations fall much more rapidly after the glucose solution than after the sodium salt. The latter, in turn, behaves like sulfanilamide. The kidney clears the glucose sulfapyridine at a rate several times that of either sodium sulfapyridine or of sulfanilamide. Indeed, the clearance of the glucose sulfapyridine given intravenously is so high as to suggest that there is no reabsorption by the tubules. This is in sharp contrast to the low clearances found after the intravenous injection of sodium sulfapyridine or of sulfanilamide which indicate considerable reabsorption of the "free" and some reabsorption of the acetylated forms of the latter compounds. The difference between the clearances of glucose sulfapyridine and of sulfanilamide was in nowise altered when the subcutaneous route was used. The blood levels attained were lower after the subcutaneous injection but in each instance they were more sustained.

Following the oral administration of the glucose-sulfapyridine, absorption is considerably delayed so that the maximum levels in the blood are reached after 24 and sometimes even after 36 hours, in contrast to four or six hours after ingestion of sulfapyridine or sulfanilamide. The levels are somewhat lower than with the two latter compounds. The results obtained for clearances when the glucose sulfapyridine is taken by mouth are essentially the same as for sulfapyridine or sulfanilamide, and not like that of glucose-sulfapyridine given parenterally.

These findings are indirect evidence that at least most of the sulfapyridine found in the blood after intravenous or subcutaneous injection of the glucose sulfapyridine solution is circulating in a different form from that found after the oral ingestion of the same material. Presumably, in the former instances the sulfapyridine is chemically combined with glucose and when it is absorbed from the bowel the compound has been hydrolyzed, leaving sulfapyridine free to act as such. Unfortunately, if this is true the method used for determining free sulfapyridine would involve hydrolysis of the compound giving values for the determination of "free" sulfapyridine, which would include any of the drug that is in combination with glucose. Furthermore, acetylation of sulfapyridine proceeded in a different manner when glucose-sulfapyridine was given by the intravenous or subcutaneous routes than when it was given orally. In the latter instance it behaved like sulfapyridine or sulfanilamide. Additional evidence indicated that the glucose sulfapyridine, when given intravenously and subcutaneously, did not distribute itself in the body fluids to the same extent as sulfanilamide or as sodium sulfapyridine.

The urine collected after parenteral glucose-sulfapyridine administration contained both free and conjugated sulfapyridine by the method used. Although large concentrations of the conjugated form were found in the urine, this was probably not the glucose compound, since it is not hydrolyzed in the

course of determining the amounts of free sulfapyridine and is not accompanied by glycosuria.

The bacteriological tests indicated that when sodium sulfapyridine is added to human blood it exerts marked pneumococcidal activity and behaves, in this respect, like equivalent amounts of sulfapyridine.<sup>12</sup> The glucose-sulfapyridine, on the other hand, showed no bactericidal or bacteriostatic activity even when high concentrations were used. When glucose sulfapyridine was added to blood and the mixture allowed to stand at room temperature, or better at 37° C., and then tested, it was found to exert bacteriostatic activity equivalent to that found with smaller concentrations of sulfapyridine. Blood withdrawn from patients after parenteral administration of the glucose-sulfapyridine solution showed no bactericidal or bacteriostatic action when tested, but, just as in the *in vitro* experiment, slight bacteriostatic action developed after standing. After the oral ingestion of this material, however, the bactericidal action of the blood was the same as that found with similar blood concentrations after the administration of sulfapyridine or its sodium salt, and corresponded to the level of free sulfapyridine in the blood.

These findings indicated that the sulfapyridine as it occurred in the glucose-sulfapyridine solution or in the blood after the parenteral injection of this solution was, for the most part, inert. The sulfapyridine found in the blood after oral ingestion was active and probably uncombined with glucose. Active material is also released when glucose-sulfapyridine is allowed to stand in freshly shed blood.

### CONCLUSIONS

Sodium sulfapyridine given intravenously is of therapeutic value and may be life-saving in selected cases. Its administration is frequently accompanied by toxic reactions, some of which may be serious.

A highly concentrated solution of sulfapyridine in 50 per cent glucose was found to be non-toxic when given parenterally. When thus given, however, it was mostly inert, whereas after oral administration it behaved like sulfapyridine, except that its absorption was delayed.

Careful clinical and biological control is just as important when new methods of administration are used for chemicals of known efficacy as when new chemicals are introduced.

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# THE TREATMENT OF LOBAR PNEUMONIA WITH SULFAPYRIDINE AND SODIUM SULFAPYRIDINE, WITH OBSERVATIONS UPON EFFECTIVE BLOOD LEVELS\*.

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SINCE the demonstration by Whitby<sup>1</sup> of the specific action of sulfapyridine against the pneumococcus, the value of this new chemotherapeutic agent in the treatment of lobar pneumonia has been the subject of extensive clinical investigation. The report of Evans and Gaisford,<sup>2</sup> describing the results of treatment of 100 patients ill with lobar pneumonia, was so impressive that a stimulus was given for a wide-spread trial of the drug in this country. Subsequent publications,<sup>3-7</sup> already voluminous, not only have confirmed the observations of Evans and Gaisford, but have established a definite place for sulfapyridine in the treatment of pneumococcus lobar pneumonia. It has been shown that the drug is effective in all types of pneumococcus pneumonia, bringing about in most instances, a rapid decline in the patient's temperature and pulse rate, and that the case fatality rate is appreciably lowered in bacteremic as well as in non-bacteremic patients. Certain toxic reactions have been encountered, notably nausea and vomiting, toxic hepatitis, hematuria, kidney stones, nitrogen retention, anuria, drug rashes, as well as central nervous system disturbances. Although distressing and sometimes severe, they have not seriously interfered with the extensive clinical use of the drug.

A satisfactory system of dosage has been difficult to establish, owing to the irregularities of absorption of sulfapyridine. Long and Feinstone,<sup>8</sup> and Stokinger<sup>9</sup> have shown that absorption from the gastrointestinal tract is slow and varies markedly among different persons on the same dosage schedule. Because of this, Long<sup>10</sup> has stated that "it is best to discuss dosage in terms of concentration of the drug in the blood." In his experience, blood concentrations of 4 to 6 mg. per cent during the first three or four days of treatment are recommended for patients moderately ill with pneumococcus pneumonia. Blood levels of 7 to 10 mg. per cent are advised for severely ill patients.

In an effort to maintain satisfactory blood concentrations, various attempts have been made to introduce the drug parenterally. Whitby<sup>11</sup> has

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described the subcutaneous or intramuscular injection of sulfapyridine in oily suspension. Barnett and his co-workers<sup>12</sup> gave the sodium salt of sulfapyridine in a 2 per cent solution by rectum to patients with pneumonia, and were able to maintain "adequate blood concentrations." Marshall and Long<sup>13</sup> were the first to publish their results on the use of sodium sulfapyridine intravenously in human beings. They recommend the giving of this salt in a 5 per cent solution at five-hour intervals to severely ill patients.

The present report records observations made on 135 patients ill with pneumococcus pneumonia. There were 110 patients treated with sulfapyridine alone; and 25 patients given sodium sulfapyridine in combination with sulfapyridine orally. We have made an attempt to determine the optimum drug concentration by a study of the blood levels achieved in the course of routine administration of sulfapyridine. We will briefly record our experiences with these drugs.

#### MATERIALS AND METHODS

In November 1938, we began the treatment of patients with sulfapyridine under the Pneumonia Control Program sponsored by the District of Columbia Health Department. The cases included in this study were for the most part treated at the Gallinger Municipal Hospital. A large number received treatment at the Emergency Hospital, under the Parmelee Pneumonia Study. A smaller number of patients were treated in other hospitals of Washington or in homes. All of the patients, however, were observed by one of us at daily intervals. Each patient was studied according to the routine of the Program, which consisted of a complete history, physical examination, sputum typing and blood culture, hemogram, and urine analysis, as well as roentgen-rays whenever possible. Blood counts were taken at frequent intervals, and blood cultures repeated as indicated. Daily blood sulfapyridine determinations were made on many of the recent cases. Treatment was instituted only after a satisfactory sputum typing had been accomplished.

Owing to the limited supply of the drug on hand when this study was begun, a certain selection of cases was necessary. Accordingly, alternate patients with Type I pneumococcus pneumonia were given type-specific horse or rabbit serum. A few patients with pneumococcus pneumonia caused by the "higher types" were given rabbit serum sent to us for experimental trial. A total of six patients were given type-specific antiserum in addition to sulfapyridine and are the only serum-treated cases included in this study. All other patients, irrespective of type, received the drug.

When a supply of sodium sulfapyridine became available, this was given intravenously in conjunction with sulfapyridine orally. Twenty-five patients received the former drug according to the technic recommended by Marshall and Long.<sup>13</sup> In some instances sodium sulfapyridine was given prior to commencing oral therapy, in order to study the blood concentration. On other occasions it was given subsequent to oral therapy when the blood levels were found to be low.

At the beginning of this study, sulfapyridine was given in initial doses of 2 grams statim, followed by 1 gram at four-hour intervals, until the temperature had been normal for 48 to 72 hours. The initial dose was subsequently increased to 4 grams and the drug continued as before during the critical period. After 48 to 72 hours the drug was reduced to 1 gram every six hours, maintained at this for another 48 to 72 hours, then further reduced to 0.5 gram every four hours for a similar period.

Sodium sulfapyridine was given intravenously as a 5 per cent solution in distilled water or physiological saline. The usual dose administered to an adult of average size was 3.8 grams. For undersized individuals, 0.05 gram per kilogram of body weight was the dosage adopted. The solution was administered slowly over the course of 10 to 12 minutes, care being taken that none of the material escaped outside the vein.

Blood sulfapyridine determinations were made by Marshall's method, previously described for sulfanilamide.<sup>14, 15</sup>

There were 122 patients in whom a diagnosis of pneumococcus lobar pneumonia was made, and 13 patients in whom bronchopneumonia, or atypical pneumonia, was found. Atypical pneumonias of possible virus etiology have been excluded from this series.

## RESULTS

*Age Group, Sex, Race:* In table 1 are given the age, sex, and race distribution of the 135 cases studied. The frequency of pneumococcus pneumonia in the younger age groups, and in males, is demonstrated. The preponderance of colored over white patients must be qualified by annual census figures from Gallinger Municipal Hospital. These have shown a ratio of 60-40 in favor of colored patients.

TABLE I  
Distribution of 135 Cases According to Age, Sex, Race

Age	Sex and Race
10-19.....14 cases	Male white.....33 cases
20-29.....32 cases	Male colored.....53 cases
30-39.....35 cases	
40-49.....22 cases	Female white.....25 cases
50-59.....14 cases	Female colored.....24 cases
60-69.....10 cases	
70-79.....6 cases	
80-89.....2 cases	

*Incidence of Types, Bacteremia, Deaths:* There were 114 patients in whom a single pneumococcus type was isolated from the sputum. In 21 additional patients more than one type was obtained by the Neufeld reaction. Because of the difficulty of classification, these have been included in table 2 under a separate heading. The frequency of pneumococcus types found in this series correlates closely with previous findings of Dowling and Aber-

nethy.<sup>10</sup> Of interest is the fact that Type II is relatively infrequent as a cause of pneumococcus pneumonia in Washington. In the majority of instances, Types I to VIII pneumococcus were found, 58 per cent of the cases being caused by these types.

TABLE II  
Incidence of Types, Bacteremia, Deaths

Type	No. Cases	Bacteremia	Deaths
<i>Single Types</i>			
I.....	23	7	0
II.....	7	2	1
III.....	22	2	2
IV.....	8	2	1
V.....	1	0	0
VI.....	2	0	0
VII.....	8	2	0
VIII.....	8	2	2
IX.....	3	0	0
X.....	2	0	0
XI.....	1	0	0
XII.....	1	0	0
XIII.....	2	0	0
XIV.....	5	0	1
XV.....	1	0	0
XVI.....	2	0	1
XVII.....	1	1	0
XVIII.....	4	1	1
XIX.....	3	0	0
XX.....	1	0	0
XXI.....	3	0	1
XXII.....	3	1	3
XXIV.....	2	0	0
XXVII.....	1	0	0
<i>Multiple Types</i>			
IV, VI.....	1	0	0
XVI, XX, XXXI.....	1	0	0
III, VII, XXI.....	1	0	0
XVII, XXXII.....	1	0	0
XXIX, XIV.....	1	0	0
X, XIII, XXVIII.....	1	0	0
III, X, XI, XVI, XVII.....	1	0	0
III, VIII.....	1	0	0
XII, XVIII.....	1	0	0
XVIII, XIX, XXI, XXIII, XXV.....	1	0	0
VI, XVIII.....	1	0	0
III, XI, XVI.....	1	0	0
I, VII, XX.....	1	1(XX)	1
IX, XIII.....	1	0	0
XVIII, XI, XX.....	1	0	0
VII, XIII.....	1	1(XIII)	0
VII, VIII.....	1	1(VII)	0
XIV, XV.....	1	0(VIII)	0
III, XVII.....	1	0	0
III, XIX.....	1	0	1
III, IX.....	1	0	0
Total.....	135 Cases	23 Bacteremia	15 Deaths

% Bacteremia (among 122 cases).....18.8%  
% Died.....11.1%

Blood cultures were taken on 122 patients. In 23 of these, bacteremia was discovered (18.8 per cent). This low incidence may be explained in part by the fact that most of these cultures were transferred for study to the Health Department laboratory, which is located some distance from the Municipal Hospital. We do not believe that the cases seen in Washington during the past season were any less severe than in former years.

There were 15 deaths in this series, or a case fatality for the whole series of 11.1 per cent. No patients were excluded from the study because of insufficient treatment. The proportion of deaths among 99 non-bacteremic cases was 8 per cent; among 23 bacteremic cases, 21 per cent. An analysis of the deaths is given in table 3.

*Effects of Therapy on the Clinical Course:* As have others,<sup>3-7</sup> we found a rapid fall in the temperature and pulse rate with sulfapyridine. In 93 patients the temperature fell by crisis to 100 degrees in an average time of 16 hours from the beginning of therapy. This group includes cases treated early as well as late in the course of the disease. In 23 patients defervescence occurred by lysis over a period of 48 hours or longer. In 19 patients we were unable to observe that the drug exerted any beneficial effect upon the febrile course of the disease. Although, in most cases, with the decline in temperature there was a rapid amelioration of symptoms, these findings were not so constant as seen in patients treated with type-specific serum. We would agree with Finland<sup>7</sup> that patients treated with sulfapyridine alone manifest evidence of illness for a considerably longer period of time. It has not been unusual, in our experience, to observe symptoms of intoxication which persist for two to four days after the temperature has become permanently normal.

We have seen numerous instances of rapid resolution of the pneumonic consolidation. In other instances resolution has proceeded at an unusually slow rate. Similar to the findings of others, we have observed six cases of relapses or recurrence occurring when the dosage was reduced before resolution was well advanced. In addition, we have seen reinfection with a different type of pneumococcus in three patients, within four to six weeks after complete recovery from the original attack of pneumonia. Our data on the immune response of patients treated with sulfapyridine alone indicate that type-specific immunity for the infecting pneumococcus develops at or about the time of recovery.

*Dosage:* The amount of drug given each patient varied considerably, depending upon the presence or absence of toxic symptoms and the clinical response elicited. In the early part of this study a dosage of 2 grams was given initially. In the more recent cases, where particular attention has been paid to blood concentration, larger doses have been given initially (4 grams) and oral therapy has been supplemented with intravenous injections of sodium sulfapyridine. The average total dosage given to these 135 patients was 29.6 grams.

*Complications:* Six patients developed pleural effusion during or sub-



TABLE III  
Analysis of Deaths

No.	Age	Type	Bact.	No. Lobes Involved	Adm. W.B.C.	Day of Adm.	Day Rx Begun	Total Dosage Grams	Remarks
1	45	IV	0	1	12,000	1	4	21	Fractured skull. No response to Type IV rabbit serum.
2	61	XXI	0	2	6,400	1	4	4	Bronchopneumonia following operation for cancer stomach. Co-existing tbc.
3	45	XIV	N.D.*	1	28,000	6	6	5	Uremia.
4	15	XVI	0	2	18,000	1	4	8	Congenital heart disease with congestive failure.
5	23	XXII	0	1	7,000	3	4	25	Anemia before treatment, accentuated by sulfapyridine.
6	53	VIII	0	2	30,000	7	8	30	Diabetes, hypertension. No response to 240,000 U. rabbit serum.
7	40	XXII	+	3	22,600	6	7	21	C-V renal disease. Uremia.
8	43	III	0	2	25,300	6	8	50	Rheumatic heart disease. Congestive failure.
9	66	I, VII, XX	+	3	15,000	6	10	63	No response to Type I or VII serum. Developed empyema.
10	75	IX	+	2	6,600	2	2	12.2	C-V renal disease, circulatory failure during serum administration.
11	70	XVIII	N.D.*	2	13,000	5	5	4.8	Moribund on admission. Uremia.
12	52	III, XIX	0	1	22,000	?	?	7.6	Moribund on admission.
13	32	VIII	+	3	9,350	1	10	33.6	Delirium tremens. No response to 900,000 U. rabbit and horse serum.
14	55	XXII	+	2	13,000	5	5	20.3	Congestive heart failure. ? Underlying tuberculosis.
15	39	II	+	1	?	2	3	6	Moribund on admission.

\* Blood culture not done.

sequent to their acute febrile period of illness (an incidence of 4 per cent). Diagnostic thoracentesis was performed in these patients as soon as the fluid was detected by physical examination or roentgen-ray. Subsequent removal of the fluid was performed as indicated by the clinical condition of the patient. If respiratory embarrassment was present, an attempt was made to remove all of the fluid. Empyema occurred in five patients (incidence of 3.7 per cent). The pneumococcus types isolated from these empyemata were: Types V, VII, IX, XVII and XX. It is interesting to note that in none of the 23 cases of Type I pneumonia did empyema develop. No other complications were present in this series.

#### OBSERVATIONS UPON BLOOD CONCENTRATION

In 65 of the 135 treated cases, observations have been made upon the blood levels. These were made in the majority of instances at daily intervals during the acute febrile period and up to the time convalescence was established. A total of 250 separate determinations of the "free" sulfapyridine concentration in the blood was made, or an average of almost four determinations per patient.

A correlation of the mean blood concentration with the clinical response obtained has been attempted. In table 4 are summarized the therapeutic effects according to certain groupings of the mean blood levels.

TABLE IV  
Relationship of Clinical Response to Mean Blood Concentration

Blood Concentration	Number of Patients	Recovered	Died	Clinical Response			
				Crisis	% Crisis	Lysis	No Effect
Group I—0-2.9 mg. %	18	17	1	13	66	3	2
Group II—3-5.9 mg. %	27	24	3	17		5	5
Group III—6-8.9 mg. %	13	12	0*	13*	90	0	0
Group IV—9-11.9 mg. %	7	6	1†	5		1	1†

\* Includes one patient who obtained excellent response to drug, but died later of cardiac failure.

† Denotes patient with diabetes and severe Type VIII infection. Obtained no response to serum or drug.

It will be seen that the largest number of patients are included in Groups I and II, those whose mean blood levels were 5.9 mg. per cent or below. A large number of recoveries took place in these two groups of patients, which corresponds to the findings of other investigators<sup>5-7</sup> who have reported excellent clinical improvement in patients whose blood levels were low. The number of recoveries was also large in Groups III and IV, where the mean blood level was 6 mg. per cent or above. There were fewer deaths in the latter two groups, only one of which could be attributed to failure of the drug.

The manner of clinical response demonstrated even more striking differences among the four groups. In Groups I and II there was the smallest percentage of patients exhibiting the phenomenon of crisis, and the largest number of those in whom the drug exerted little or no effect upon the temperature ("lysis" or "no effect"). By contrast, in those patients whose blood levels were 6 mg. per cent or above, there were only two whose response was not satisfactory. An explanation of the failure of patients to respond to sulfapyridine therapy was not clear in every case. In some patients nausea and vomiting interfered with absorption of the drug and, consequently, effective blood levels were not achieved. In others, complicating factors were present which might have interfered with the response. In some patients there was no obvious cause for the failure to achieve a satisfactory result. An analysis of these factors is given in table 5.

TABLE V  
Analysis of Cases Showing Poor Response to Therapy

Group	Case	Manner of Response	Remarks
I (0-2.9 mg. %)	1	Lysis	Nausea and vomiting.
	2	Lysis	Nausea and vomiting: leukopenia.
	3	Lysis	Pleural effusion.
	4	No effect	Diarrhea, anemia, pleural effusion.
	5	No effect	Moribund on admission.
II (3-5.9 mg. %)	6	Lysis	No obvious cause.
	7	Lysis	No obvious cause.
	8	Lysis	No obvious cause.
	9	Lysis	No obvious cause.
	10	Lysis	Pleural effusion.
	11	No effect	Nausea and vomiting: pleural effusion.
	12	No effect	Severe anemia: leukopenia.
	13	No effect	C-V-renal disease: uremia.
	14	No effect	Empyema.
	15	No effect	Empyema.
IV (9-11.9 mg. %)	16	Lysis	No obvious cause.
	17	No effect	Severe diabetes. No response to serum.

Although the number of cases in this series is small, the observations suggest that mean blood levels of 6 mg. per cent or above are desirable in patients being treated with sulfapyridine.

#### USE OF SODIUM SULFAPYRIDINE

While this work was in progress, Marshall and Long<sup>13</sup> reported upon the use of sodium sulfapyridine in 30 patients with pneumococcus pneumonia. Indications for giving this compound to patients were two-fold: first, the finding of low blood concentrations, usually the result of faulty absorption from nausea and vomiting, with poor clinical response; and second, unusual severity of the pneumococcus infection. They have shown that blood levels

of 5 to 8 mg. per cent can be attained with rapidity and maintained for at least four hours. In their experience, patients given sodium sulfapyridine intravenously, in combination with sulfapyridine orally, obtained excellent clinical responses.

A preliminary note of our use of this new compound in the treatment of 10 patients has been reported.<sup>17</sup> Up to the present time, we have given sodium sulfapyridine, in one or more intravenous injections, to 25 patients with pneumococcus pneumonia. These are included in the 135 cases reported above. This therapy has been supplemented with the oral administration of sulfapyridine.

A few of the early cases were given the sodium salt only after the previous administration of the oral preparation had resulted in low blood concentration or poor clinical response. The most recent cases have been given one injection of sodium sulfapyridine upon admission and sulfapyridine started by mouth simultaneously.

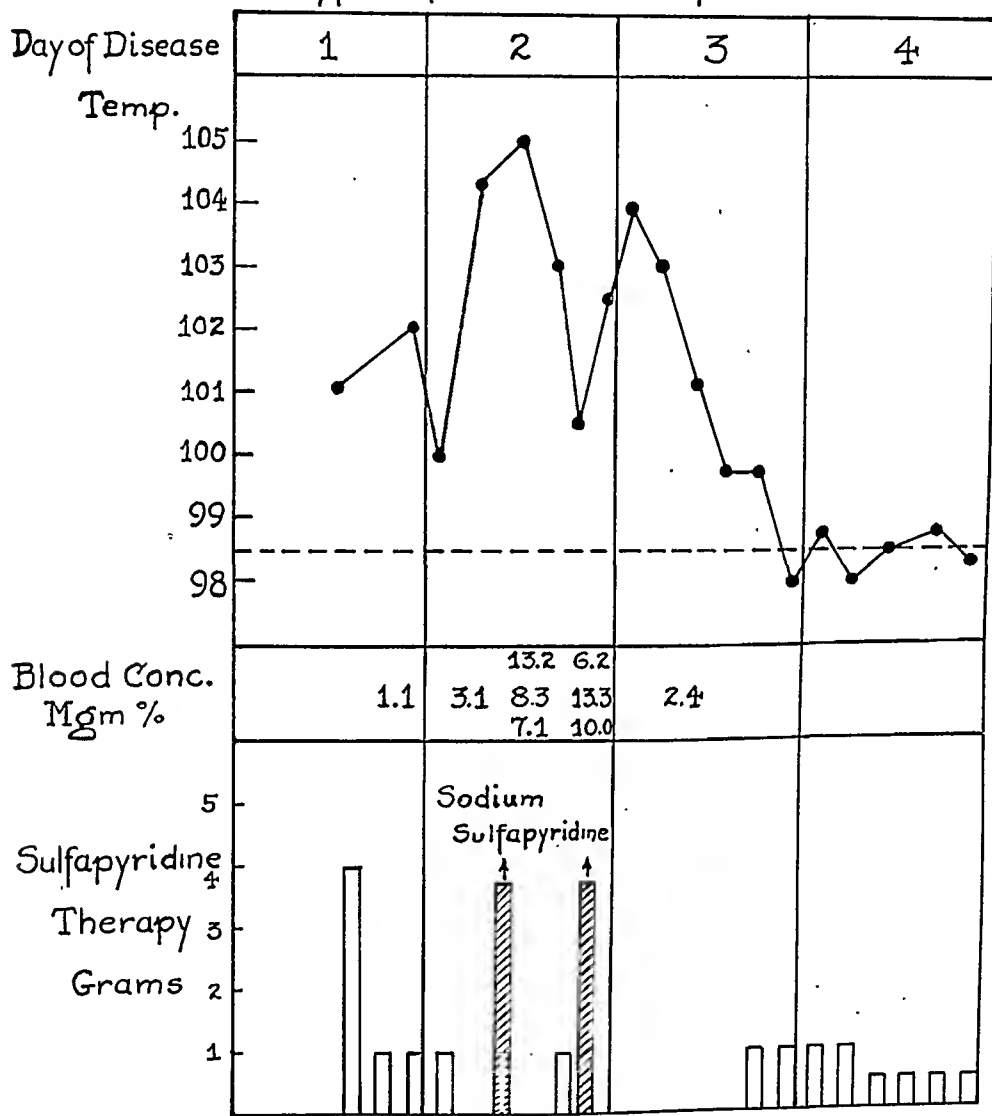
The type of response elicited in these two groups of patients is portrayed graphically in charts 1 and 2.

Chart 1 is the clinical record of a 29-year-old white male with Type I pneumococcus pneumonia of the right upper lobe. He was admitted to the hospital at the end of the first day of disease. Leukocytes were 29,700. The admission blood culture proved sterile. He was moderately ill. Oral sulfapyridine therapy was begun with 4.0 grams initially, followed by 1.0 gram at four-hour intervals. With administration of the third dose, he vomited a considerable portion of the previous medication and further oral therapy was temporarily stopped. Five hours after starting sulfapyridine therapy the blood concentration was only 1.1 mg. per cent, and by the following morning was 3.1 mg. per cent. There had been no appreciable effect upon his clinical course. He was then given 3.8 grams of sodium sulfapyridine intravenously. At the completion of injection the patient vomited. The blood level rose to 13.2 mg. per cent in five minutes, dropped progressively to 8.3 mg. per cent in one hour, 7.1 in three hours and 6.2 in seven hours. A second injection of sodium sulfapyridine was then given, with another prompt rise in the blood concentration to 13.3 mg. per cent and a gradual fall over a period of nine hours to 2.4 mg. per cent. After the first injection, there was a precipitous fall in temperature to 100.4° F. which was not sustained. After the second injection, the temperature fell to normal by crisis. Nausea and vomiting persisted for several hours. Convalescence was uneventful.

The patient represented in chart 2 was a 40-year-old colored female admitted to the hospital on the third day of disease. Consolidation of the lower left lobe was found. Pneumococcus Type II was obtained from the sputum by mouse inoculation. Blood culture proved sterile. The day after admission, the fourth day of disease, the patient was given 3.8 grams of sodium sulfapyridine intravenously. There was considerable nausea at completion of the injection, but no vomiting. The blood levels recorded were

9.4 mg. per cent in one hour, and 7.5 mg. per cent in four hours. Two grams of sulfapyridine were given orally at the beginning of this injection and continued in doses of 1.0 gram every four hours. During the course of this day the temperature fell by crisis to 100° F. in 12 hours. The following day the patient was given another injection of 3.8 grams intravenously be-

W. P. & W. 29. Type I pneumococcus pneumonia



### CHART I.

cause of the low blood level (1.2 mg. per cent), evidently the result of vomiting during the night. Following this second injection, there was again prompt rise in the blood level to 13.1 mg. per cent which fell to 4.8 in seven hours and was accompanied by marked clinical improvement. Sulfapyridine was continued during the next 48 hours, up to a total of 22 grams. The patient made an uneventful recovery.

A summary of our experiences with sodium sulfapyridine is given in table 6. A discussion of the toxic reactions to this salt will be given below. As yet, the number of cases so treated is too small to justify any statistical study of the case fatality rate. However, our observations have shown that

### M.B. ♀. C. 40. Type II pneumococcus pneumonia

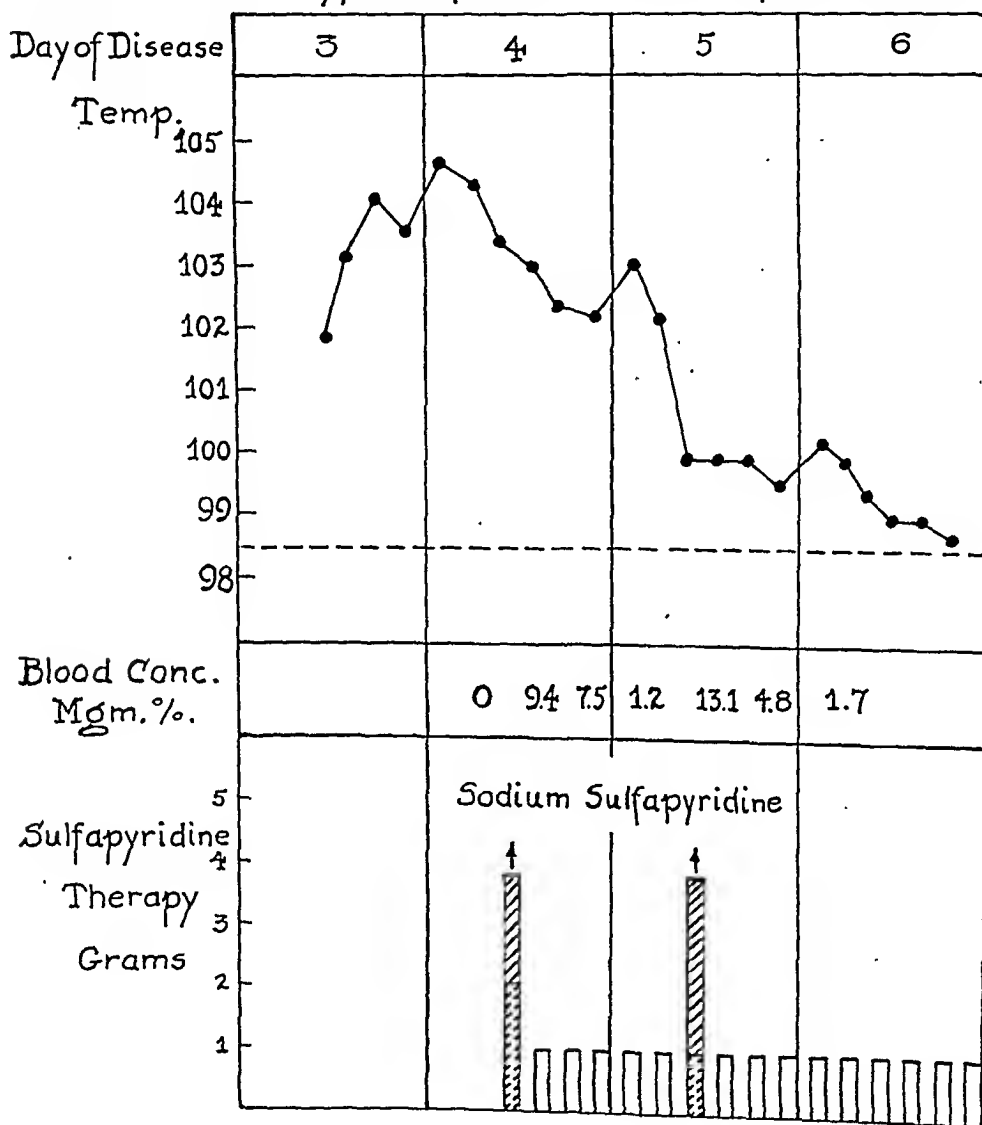


CHART II.

the intravenous administration of sodium sulfapyridine is an effective means of attaining high blood levels rapidly and that these can be maintained for several hours. The clinical response of patients who have received this drug is often dramatic.

TABLE VI  
Results of the Intravenous Injection of Sodium Sulfapyridine

Blood Concentration—mg. per 100 cubic centimeters																
Case No.	Color Sex Age	Type	Bact.	Dose	Be- fore	Time after end of injection								Reactions	Remarks	
						5 min.	10 min.	20 min.	30 min.	1 hr.	2 hrs.	3 hrs.	4 hrs.			Later
1	W-M-36	V	0	3.8	4.0*		7.6	7.7	7.8						Nausea and vomiting Transient hematuria	Empyema—Recovery
2	W-F-14	I	0	3.0	6.4*		10.8							1-4, 1.0	Chill	Uneventful recovery
3	W-M-29	I	0	3.8 3.8	3.1* 6.2*	13.2 13.3				8.3	7.1 10.0			2.4	Nausea and vomiting None	Uneventful recovery
4	W-M-58	I	+	3.3	3.8*		16.7			11.0	9.6	8.8	12.4		None	Uneventful recovery
5	W-F-75	III	+	2.2	8.5*		21.4			14.1	14.0	13.8			None	Death during serum admin- istration
6	C-M-32	VIII	+	3.4	0†		6.8			6.0	5.7	5.5	5.9	5.6, 6.4 8.4, 6.0	None	Severe infection. Delirium tremens. 900,000 U. serum previously without effect. Death
7	C-M-29	I	0	3.9	0†		7.0			5.7	4.5	3.8	3.6	7.3, 3.2	None	Uneventful recovery
8	C-M-22	I	0	3.8	0†		7.8			17.18	7.4	3.6	3.8	3.6, 5.0, 2.4	Nausea and vomiting	Uneventful recovery
9	C-F-40	II	0	3.8 3.8 1.2	0† 1.2					9.4 13.1			7.5	4.8, 1.2, 3.6	Nausea and vomiting Nausea and vomiting	Uneventful recovery
10	C-M-44	III	0	3.8	0†					6.1			4.5	3.8, 3.9, 3.7 2.8	Nausea and vomiting	Uneventful recovery
11	C-M-45	I	0	3.8	0†					5.6			7.5	4.3, 3.6, 2.5	Slight nausea	Uneventful recovery
12	C-F-25	XIV	0	2.7	2.5*		6.5							2.2	None	Uneventful recovery

TABLE VI—Continued

Case No.	Color Sex Age	Type	Bact.	Dose	Blood Concentration—mg. per 100 cubic centimeters										Reactions	Remarks
					Be- fore	Time after end of injection										
						5 min.	10 min.	20 min.	30 min.	1 hr.	2 hrs.	3 hrs.	4 hrs.	Later		
13	C-M-70	XVIII	0	3.8	0†		5.0			4.4					None	Moribund on admission
14	C-F-30	IV	0	2.8	0†		8.0			6.0	6.0		5.1	1.8	None	Uneventful recovery
15	C-M-35	IX	0	3.8	0†					3.5				2.3, 1.8 4.7, 4.0	None	Uneventful recovery
16	C-M-33	XVI		3.5	0†		6.6			6.0			7.2	9.0, 9.0	None	Uneventful recovery
17	W-M-34	XIX	0	3.8 3.8	0† 5.1		4.4			4.4				6.0	Slight nausea and vomit- ing	Uneventful recovery
18	C-F-22	X	0	3.8 3.8	0†					8.0				8.9, 6.0	None	Uneventful recovery
19	C-F-52	XIX	0	3.8 3.8	0		11.4			11.4	9.0 11.4		11.4		None	Moribund on admission
20	C-M-58	VII	+	3.8	0*		4.8				4.2		4.0	5.1, 4.8, 3.8	None	Emyema, recurrence, recov- ery
21	C-M-42	II	0	3.8 3.8	3.6* 8.9					8.9 8.9	10.0		6.1 5.7	5.7	Gross hematuria	Severe infection. No re- sponse 600,000 U. serum previous to drug therapy. Death.
22	W-F-34	XIV, XV	0	2.6	0†		4.0			3.6			4.0	6.0, 7.2	Nausea and marked men- tal confusion	Uneventful recovery
23	C-M-42	XIV	0	3.5 3.5	9.0									2.7, 10.0, 10.0	Nausea and vomiting	Uneventful recovery
24	C-F-55	XXII	0	3.8	0					5.4			6.4	6.4, 9.0	None	Congestive heart failure on admission. Death
25	C-M-35	II	0	3.0 3.0	0† 3.0		15.0			5.0 12.5	4.4	3.9	3.8 11.0	3.4 12, 10, 9.5	Slight nausea, vomiting None	Drop in PMN over course of 3 days from 87% to 29%

\* Denotes sulfapyridine administered orally prior to injection of sodium salt.

† Denotes sulfapyridine administered orally simultaneously with injection.



## TOXIC REACTIONS

A summary of the toxic reactions noted in this series of 135 cases is given in table 7. The reactions encountered with the use of sodium sulfapyridine in 25 cases have been outlined above (table 6). Most of these findings have been previously described by others.<sup>5-7, 10, 13</sup> We have found gastrointestinal symptoms to be the most frequent reaction, occurring in 34.7 per cent of all cases. In those patients treated with the sodium salt, 10, or 40 per cent developed either nausea alone, or nausea with vomiting, following the injection of the drug. In our experience, sulfapyridine therapy has had to be stopped only rarely because of these gastrointestinal disturbances. Temporary discontinuance of the drug, administration of the crushed tablets in milk, the giving of aluminum hydroxide preparations after each dose, and the intravenous injection of 5 per cent or 10 per cent dextrose all have been of value in alleviating these unpleasant symptoms.

Mild reduction of the red blood cells and hemoglobin values were noted in four patients. These required no treatment. Severe hemolytic anemia developed in one patient with a preëxisting anemia, and was principally responsible for her death. Another patient developed an acute hemolytic anemia during therapy, which responded promptly to transfusion. Leukopenia and granulocytopenia were each observed in two patients. In none of these, however, did agranulocytosis occur.

TABLE VII  
Toxic Reactions in 135 Cases

Reaction	Number	Incidence—%
Nausea, alone . . . . .	15	11.1
Nausea and vomiting—mild . . . . .	17	12.5
—severe . . . . .	15	11.1
Diarrhea . . . . .	1	0.7
Hemolytic anemia—mild . . . . .	4	2.9
—severe . . . . .	2	1.4
Leukopenia . . . . .	2	1.4
Granulocytopenia . . . . .	2	1.4
Hematuria . . . . .	2	1.4
Toxic psychosis . . . . .	3	2.2
Dermatitis . . . . .	4	2.9
Drug fever . . . . .	3	2.2

In 14 of the most recent cases, determinations of the non-protein nitrogen were performed at daily intervals. An elevation of 10 mg. per cent above the normal (25–35 mg. per cent) was observed during the course of therapy in 11 of these patients, all of whom subsequently recovered. In one patient who was under observation for chronic glomerular nephritis and who developed a Type XVIII pneumococcus pneumonia, there was considerable nitrogen retention and exacerbation of nephritis when sulfapyridine therapy was instituted. The non-protein nitrogen rose from a level of 64 mg. per cent before therapy to 120 mg. per cent after nine grams of the drug had been given over a period of 48 hours.

Hematuria was noted in two patients, both of whom received sodium sulfapyridine intravenously. In one of these patients the hematuria was transient and did not interfere with subsequent recovery. The other patient developed hematuria seven hours before death, which may have contributed to his demise. No cases of kidney stones have been observed by us.

Cyanosis of an extreme degree was seen in eight patients (5.8 per cent), but because of the difficulty of evaluating this sign in the presence of pneumonia it has been omitted from the tabular summary. Toxic psychoses were observed in three patients and were thought to be due to the drug.

Dermatitis, characterized by a diffuse morbilliform eruption, was noted in four cases (2.9 per cent). This eruption, similar to that seen in cases treated with sulfanilamide, appeared 8, 11, 11 and 12 days, respectively, after the beginning of therapy, lasted 3 to 4 days, and in three instances was accompanied by an exacerbation of temperature.

#### COMMENT

The results of the above study, conducted over a period of eight months, demonstrate the value of sulfapyridine in the treatment of pneumococcus pneumonia. The mortality rate of 11.1 per cent for the entire series of 135 cases is at variance with other published reports. Pepper and colleagues<sup>6</sup> have shown a mortality of 7 per cent among 400 cases of typed pneumococcic pneumonia. Finland et al.<sup>7</sup> found a case fatality rate of 15 per cent in 95 patients of a comparable age group. Although these variations have been found, it should be noted that each of these studies represents less than one year's experience. Not until the drug has been given over several seasons to considerably more cases will a figure representing the true case fatality rate be obtained. We believe, however, that in the future, unless critical attention is paid to the diagnosis of pneumonia and to the proper selection of patients for treatment, a false and too optimistic view of the therapeutic effects may result.

A comparison of sulfapyridine treated cases with those receiving type-specific serum is outside the scope of this communication. Such an analysis will be the subject of a subsequent report. Suffice it to say that the results here obtained compare favorably with those found in our serum-treated cases. It is interesting to note that in the period covered by this study, there were no deaths in 23 Type I cases. In the period between January 1 and September 1, 1938, there were 32 Type I patients, studied under the District of Columbia Pneumonia Control Program, who received specific serum treatment.<sup>18</sup> Two of these patients died, giving a case fatality rate of 6.2 per cent. In 16 untreated patients observed simultaneously the mortality rate was 25 per cent.

Although there is a uniformity of opinion among various authors as to the method of administration of sulfapyridine, there is considerable variation in the views concerning what constitutes the optimum blood level of the drug.

Pepper et al.<sup>9</sup> have stated that simple blood level determinations have limited value because of the fact that they have observed clinical improvement in patients whose level did not exceed 2 mg. per cent. Long,<sup>10</sup> on the basis of equally wide experience, has advised keeping the blood concentration between 4 and 6 mg. per cent during the first three or four days of treatment in order to achieve the best results. On the basis of our observations we believe that frequent blood level determinations are of definite value in the treatment of these cases. Notwithstanding the fact that certain recoveries do take place in patients whose blood levels are low, we believe that results are more satisfactory if the mean blood concentration is 6 mg. per cent or above. A significant difference between the clinical response of patients having high and those with low blood levels has been shown. Whereas 90 per cent of patients with mean blood concentrations above 6 mg. per cent recovered by crisis, only 66 per cent of those with levels below 6 mg. per cent recovered in this manner. The importance of similar correlation studies between blood level and recovery is obvious.

Our studies on the soluble salt, sodium sulfapyridine, have shown that this drug is of value as a supplement to the oral administration of sulfapyridine. The rapidity with which high blood concentrations can be attained makes it particularly useful in severely ill patients in whom a speedy therapeutic effect is desired. In patients whose blood levels are low and who are not responding to the oral preparation, it is a valuable therapeutic addition. Although certain toxic reactions, notably nausea, vomiting, hematuria, have followed its use, we believe that more extended clinical trial of this drug is justified.

#### SUMMARY AND CONCLUSIONS

1. A series of 135 cases of pneumococcus pneumonia treated with sulfapyridine and sodium sulfapyridine is reported.
2. A mortality rate of 11.1 per cent was found in the entire group of patients. The incidence of death among 99 non-bacteremic cases was 8 per cent; among 23 bacteremic cases, 21 per cent. No deaths occurred in the 23 Type I treated cases.
3. The toxic reactions and the effects of therapy upon the clinical course of the disease have been discussed.
4. In a group of 65 patients, in whom 250 blood concentration determinations were done, those showing mean blood levels of 6 mg. per cent or above had a more satisfactory clinical response.
5. Our experiences with the use of the soluble sodium sulfapyridine in 25 cases have been given. The value of this drug in the treatment of severely ill patients, or in those whose response to the oral preparation is poor, has been discussed.

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## EXPERIENCES IN THE TREATMENT OF LOBAR PNEUMONIA \*

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DURING the winter of 1938-39 the opportunity was presented to study the incidence of pneumococcus infection in a group of hospitals in the St. Louis area. We also observed the therapeutic effects of type specific rabbit serum and sulfapyridine in two series of cases. In this paper no attempt is being made to review the literature nor to enter into a discussion of the mode of action of sulfapyridine. We merely desire to present two series of cases, one drug treated and one treated with type specific rabbit serum so that as other similar series are reported a composite picture may evolve which eventually will be a guide in the future treatment of pneumococcus pneumonia.

The "quellung" method of typing was used. In all, 624 type determinations were made on various materials, comprised chiefly of sputum and throat swabs but including blood cultures, pleural fluids, lung punctures, pericardial fluid and synovial fluid. This method of typing pneumococci proved very satisfactory. On 10 occasions a repetition of the test was required in order to determine the type. The direct typing failed in 59 cases where mouse culture later revealed the type. Direct typing and mouse culture disagreed in only two cases. In eight cases pneumococci were present but no type could be determined. This suggests that these eight cases were of some type other than the 1 to 30 for which we tested. Many of these examinations were made on material from patients who did not suffer from pneumococcus pneumonia.

Three hundred and forty-nine determinations were made on material from patients suffering from pneumococcus pneumonia. The incidence of the types is based on the study of this group of 349 cases. The number of cases of each type and the percentage of the whole group are shown in table 1.

Through the kindness of Dr. Joseph Bredeck and Dr. Emanuel Sigoloff of the St. Louis Department of Health we have placed for comparison the incidence of types determined in a total of 851 cases of pneumonia reported

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this winter. The greater part of this series of 349 cases was, of course, included in the total of 851 cases. It is obvious from a study of the table that the small series of 349 cases represents in fairly accurate detail the incidence of the types of pneumococci in the St. Louis metropolitan area for this year.

TABLE I  
Percentage of Incidence of Pneumococcus Types  
Series of 349 Cases. Compared with Health Department Survey,  
November, 1938 to July 1, 1939

Type	No. of Cases in Series	% Incidence in Series	% Incidence Health Dept.	Type	No. of Cases in Series	% Incidence in Series	% Incidence Health Dept.
I	65	18.6	16.6	XVI	7	2.0	0.58
I combined with other types	6	1.7	1.6	XVII	2	0.57	1.6
Total I	71	20.3	18.5	XVIII	2	0.57	1.6
II	10	2.8	2.8	XIX	16	4.5	3.6
III	38	10.8	12.2	XX	6	1.7	1.2
IV	15	4.2	5.2	XXI	1	0.28	0.9
V	30	8.5	6.2	XXII	6	1.7	0.7
VI	21	6.0	4.8	XXIII	4	1.1	2.2
VII	26	7.4	6.5	XXIV	—	—	0.82
VIII	24	6.8	8.3	XXV	6	1.7	1.0
IX	3	0.85	2.1	XXVI	—	—	—
X	3	0.85	0.82	XXVII	—	—	0.35
XI	2	0.57	1.6	XXVIII	4	1.1	0.35
XII	3	0.85	0.58	XXIX	7	2.0	1.5
XIII	6	1.7	1.6	XXX	—	—	—
XIV	4	1.1	2.5	Multiple type	30	8.5	9.04
XV	4	1.1	1.5	Types not determined	4	1.1	0.

In the study of this table it is interesting to note that Type I occurs most often, Type III with the next greatest frequency, followed by Type V. Types VII, VIII, VI, XIX, IV and II follow in the order mentioned. In four cases where there was a definite pneumonia a pneumococcus was found, but the type could not be determined. In 30 cases or in 8.5 per cent multiple types occurred. Six of these, however, were combined with a Type I organism. We observed no cases of pneumonia due to pneumococci of Types XXIV, XXVI, XXVII or XXX.

So far as therapy is concerned, this group of 349 cases of pneumonia is further divided as follows: One hundred and twenty-six cases were treated with type specific rabbit anti-serum. The types comprising this group were Types I, II, V, VII, VIII and XIV. One hundred and six cases were treated with sulfapyridine. Thirty-two cases were treated with an experimental rabbit serum which in the laboratory animal had suggested the possibility of having some "broad coverage" properties. In 85 cases not treated by the serum or the drug, the diagnosis of pulmonary involvement was verified by roentgen-ray of the lung. These cases were chiefly patients who had a definite pulmonary involvement but who were suffering in such

mild degree that no specific therapy seemed to be indicated. No deaths occurred in this group. As a rule, however, it is best to treat any case specifically as soon as the diagnosis is made, regardless of the seemingly mild clinical appearance of the infection.

### TYPE SPECIFIC RABBIT SERUM TREATED CASES

Among the 126 cases treated with type specific rabbit serum there were 10 deaths, giving a gross mortality rate of 7.9 per cent. In the detailed study of this group which follows, five cases were not included since they died under 24 hours after serum was given.

TABLE II

\*Cases not Included; Died on Day Admitted

<i>Type I</i>	
F-66—	8th day—3 lobes—bacteremia—given 400,000 Units—died 20 hrs. (SSS neg.)
M-63—	10th day—RML—empyema—bacteremia—given 140,000 Units—died 12 hrs. (SSS neg.)
F-49—	5th day—LLL—diabetic coma—bacteremia—given 140,000 Units—died 20 hrs. (no SSS)
<i>Type V</i>	
F—5—	6th day—LUL—LLL—empyema—bacteremia—given 140,000 Units—died 8 hrs. (SSS neg.)
<i>Type VIII</i>	
M-60—	8th day—2 lobes—uremia—NPN 80—bacteremia—given 180,000 Units—died 12 hrs. (No SSS)

These five cases all revealed a bacteremia and were seen late in the disease; all but one had serious complications. In three of the five deaths, the polysaccharide skin test was negative at the time of death and in two cases, the polysaccharide skin test had not yet been done at the time of death. None of these cases showed a sudden drop in blood pressure or other evidence of an immediate reaction which could have been caused by the serum administration, and so might have contributed to their sudden deaths. Since it was our feeling that these cases had not been treated adequately, we have eliminated them from the detailed analysis.

Thus we may consider a series of 121 cases of pneumonia treated with type specific rabbit anti-serum with five deaths giving a mortality rate of 4.13 per cent.

Table 3 shows this series analyzed as to type incidence, the incidence of bacteremia occurring in each type, the number of patients who recovered, the number who died, and the individual mortality rates for the various types. As is to be expected, the five deaths which occurred were all in cases with bacteremia; on the other hand, there were 14 other patients with bacteremia who recovered.

TABLE III  
121 Pneumonia Cases—Treated with Type Specific Rabbit Antiserum  
Type and Incidence—Bacteremia—Mortality Rate

Type	Total Cases	Bacteremia	No. Recovered	No. Died	Mortality Rate
I	59	8	57	2	3.38
II	13	2	12	1	7.1
V	15	5	13	2	13.3
VII	13	2	13	0	0.
VIII	19	2	19	0	0.
XIV	2	0	2	0	0.
	<u>121</u>	<u>19</u>	<u>116</u>	<u>5</u>	<u>4.13 per cent</u>

Table 4 is an attempt to analyze the series by separating the cases which were seen early enough in the disease to receive what was considered to be adequate treatment from those cases which were first seen after four days. Since none of the patients died who were seen before the sixth day, it is fair to state that no patients treated on the fifth day or sooner died, whereas five deaths occurred in patients who had received their first serum, two on the sixth, and one on the eighth, fourteenth and twenty-first days, respectively.

TABLE IV  
Relationship—Day of Disease—Serum First Given—Mortality

Type	Serum first given within 96 hrs. of onset			Serum given 96 hrs. or later after onset		
	No. Cases	No. Recovered	No. Died	No. Cases	No. Recovered	No. Died
I	38	38	0	21	19	2 { 6th day
II	9	9	0	4	3	1 { 14th day
V	6	6	0	9	7	2 { 8th day
VII	9	9	0	4	4	0 { 6th day
VIII	11	11	0	8	8	0 { 21st day
XIV	2	2	0	0	0	0
Total	<u>75</u>	<u>75</u>	<u>0</u>	<u>46</u>	<u>41</u>	<u>5</u>

Table 5 shows the relationship between the type of the organism and age of the patient and deaths. In agreement with many previous studies it was found that the deaths all occurred in patients 40 years of age or over.

TABLE V  
Relationship—Type—Age—Deaths—Serum Treated Cases

Type	Under 40 yrs.	Recovered	Died	Over 40 yrs.	Recovered	Died
I	39	39	0	20	18	2 { 57 yrs.
II	9	9	0	4	3	1 { 63 yrs.
V	8	8	0	7	5	1 { 50 yrs.
VII	8	8	0	5	5	2 { 64 yrs.
VIII	9	9	0	10	10	0 { 40 yrs.
XIV	2	2	0	0	0	0
Total	<u>75</u>	<u>75</u>	<u>0</u>	<u>46</u>	<u>41</u>	<u>5</u>



Of the 116 who recovered, 94 or 81 per cent displayed a crisis (normal temperature within 24 hour period after administration of serum). Twenty-two or 19 per cent recovered by lysis (temperature falling to normal within a period of 48 hours or longer).

Table 6 shows the incidence and extent of the immediate reaction to the administration of rabbit serum. We observed a sharp reaction in three patients, two of whom recovered. Since the other patient who ultimately died lived for 14 days following the administration of the serum, it is our feeling that death could not be attributed to shock or serum administration. This patient at autopsy showed a complicating endocarditis with vegetations on the aortic valve and was also a chronic alcoholic; he had received 280,000 units of serum.

TABLE VI  
Incidence of Immediate Reaction to Intravenous Rabbit Serum

Type	Recovered			Died			Total Cases	Total Reactions
	Mild	Moderate	Severe	Mild	Moderate	Severe		
I	19	7	1	1	0	1 (lived 14 days)	59	29
II	2	2	1	0	0	0	13	5
V	7	3	0	0	1 (lived 7 days)	0	15	11
VII	2	2	0	0	0	0	13	4
VIII	5	1	0	—	—	—	19	6
XIV	1	0	0	—	—	—	2	1
Total	36	15	2	1	1	1	121	56 or 46.2 %

Mild—37 or 30.5%      Moderate—16 or 13.2%      Severe—3 or 2.4%  
Mild—chill—less than 1° temp.      Moderate—chill—more than 1° temp.      Severe—shock.

Table 7 shows the incidence of serum sickness in the 116 patients who recovered. By "mild" it is meant that the patient had scattered urticaria. By "moderate" we indicate urticaria and one to two degrees of fever with joint pains lasting not more than 48 hours. By "severe" we indicate those who had more severe urticaria combined also with fever and swelling of the joints, the duration of which was more than 48 hours.

It is interesting to note that the total incidence of 25.8 per cent serum sickness is considerably lower than the incidence formerly associated with the administration of horse serum.

It would appear that there was some factor in the type specific serum for types V and VII which tended to cause these severe reactions as none occurred with the use of Types I, II, VIII, and XIV serum. All of the sera were adequately tested for thermal reactions before being used clinically and were found satisfactory.

TABLE VII  
Incidence Serum Sickness—116 Patients Who Recovered

Type	Total No. of Cases	Mild Reaction	Moderate Reaction	Severe Reaction
I	57	10	5	0
II	12	1	0	0
V	13	2	1	2
VII	13	2	0	3
VIII	19	4	0	0
XIV	2	0	0	0
Total	116	19	6	5

Total of 30 cases of serum sickness—incidence 25.8 per cent.

#### TECHNIC OF SERUM ADMINISTRATION

After typing of the sputum which was obtained after the patient had washed the mouth thoroughly with normal saline solution, the tests for sensitivity to rabbit serum were performed. One-tenth c.c. of a 1:100 or a 1:10 dilution of normal rabbit serum in physiological saline was injected intracutaneously on the forearm and one drop placed in the conjunctival space of one eye. The absence of conjunctivitis was noted before this was done, and a careful history regarding allergy or previous serum administration was obtained. Epinephrine 1:1000 in a hypodermic syringe was ready for use before the tests were done. If the tests were negative after 15 minutes, 1 c.c. of a 1:10 dilution of the therapeutic serum was given intravenously, slowly, over a period of five minutes. The blood pressure and pulse were noted before and five minutes after this was given, and the blood pressure cuff was left in place to facilitate readings every few minutes during the next hour. If there was no reaction or fall in blood pressure exceeding 20 mm. mercury, the balance of the serum was then given slowly by the gravity method, allowing at least one hour for 100 c.c. of serum, which amounted in most instances to 100,000 units.

If a drop in blood pressure of more than 20 mm. Hg occurred, or if the patient had any increase in respiratory difficulty and/or pulse rate increase of more than 30 beats per minute, the injection was stopped and epinephrine was given. Although a significant drop in blood pressure occurred in several cases, it was possible to continue the administration of serum cautiously after a few minutes' interval. Only in the presence of hives or severe respiratory distress and fall in blood pressure was epinephrine necessary. In many cases aspirin was given before the serum. It was felt that perhaps the aspirin decreased the severity but did not affect the incidence of chill and thermal reactions. No controlled study was made of the effect of aspirin. There was no appreciable difference in reaction or therapeutic efficiency in cases where the serum was given diluted with 200 c.c. of normal saline or when given in concentrated form.

Table 8 indicates the amount of serum administered in the group of cases.

The total is being presented merely to show the relatively small dosage used as compared with recent recommendations. It is our belief that the use of the type specific polysaccharide skin test which was used routinely in all the serum treated cases enabled us to gauge the optimum dosage of serum therapy, thus effecting a considerable saving of serum. The application of the polysaccharide skin test in this respect is more fully discussed in another report, which has been accepted for publication in the Journal of the American Medical Association.

TABLE VIII  
Pneumonia Cases Treated—Specific Rabbit Antiserum  
Amount of Serum Administered—Number of Doses

Type	Average Amount—Units	Limits—Units	Average No. Doses	Limits
I	116,000	40,000–280,000	1.6	1–6
II	160,000	120,000–340,000	1.8	1–6
V	160,000	100,000–360,000	2.0	1–6
VII	125,000	80,000–220,000	1.5	1–3
VIII	117,000	60,000–220,000	1.3	1–3
XIV	90,000	80,000–100,000	2.0	1–3

No figures are being presented as to the length of stay in the hospital because the different economic conditions encountered made such figures worthless. The well-to-do patients could go home early and receive adequate care, or stay longer with special nursing as they desired. The poor patients were kept in the hospital only as long as necessary.

#### INCIDENCE OF COMPLICATIONS

In this series of 121 cases the complications due to pneumococcus invasion elsewhere than the lungs consisted of 12 cases of empyema; 9 type I; 1 type II; 2 type V. Of these, one patient of the type I group died. There was one case complicated by otitis media occurring in the type I group, with complete recovery. There were two cases of endocarditis, both of whom died. One occurred in the type I group and one occurred in the type V group. The type V case also had empyema which was not included in the 12 cases of empyema recorded above. Four of the five deaths in the total series were in cases presenting complications.

#### SULFAPYRIDINE TREATED CASES

The series of 143 cases of pneumonia comprised 106 noted previously in this report in the discussion of the general type incidence of pneumococcus pneumonia and 37 additional untyped cases of pneumonia proved by clinical signs and roentgen-ray of the chest. The majority of these 37 cases were in infants and children; smears had shown the presence of pneumococci in all but six. Pneumonia in these six cases may have been due to organisms or virus other than pneumococcus but since no deaths occurred among the six, they are included in the series. The one death listed in this group of 37

cases was in an elderly man of 79 years with myocarditis, and autopsy showed pneumococci by smears but cultures were not done.

In the series of 143 there were 13 deaths giving a gross mortality rate of 9.09 per cent. One case is not included in the detailed study below as she was admitted in a moribund state and died shortly after admission. This patient was a female 60 years of age, admitted on the sixth day of disease with left lower lobe involvement. Later information revealed that she had a bacteremia with a Type III pneumococcus. She was given 4 grams of sulfapyridine but died within six hours.

TABLE IX  
Sulfapyridine Treated Cases—Type Incidence—Mortality Rate

Type	No. Cases	Bacteremia	Recovered	Died	Mortality Rate
I	8	0	8	0	0.0
II	1	0	1	0	0.0
III	25	3 (1 recovered)	21	4	16.0
IV	8	0	8	0	0.0
V	8	1 (died)	7	1	12.5
VI	7	0	6	1	14.3
VII	4	0	3	1	25.0
VIII	6	0	5	1	16.6
IX	2	0	2	0	0.0
X	1	0	1	0	0.0
XI	1	0	1	0	0.0
XII	1	0	0	1	100.0
XIII	1	0	0	1	100.0
XIV	3	0	3	0	0.0
XV	1	0	1	0	0.0
XVI	3	0	3	0	0.0
XVII	2	0	2	0	0.0
XVIII	2	1 (died)	1	1	50.0
XIX	8	0	8	0	0.0
XX	0	0	0	0	0.0
XXI	1	0	1	0	0.0
XXII	0	0	0	0	0.0
XXIII	0	0	0	0	0.0
XXIV	0	0	0	0	0.0
XXV	2	0	2	0	0.0
XXVI	0	0	0	0	0.0
XXVII	0	0	0	0	0.0
XXVIII	0	0	0	0	0.0
XXIX	2	0	2	0	0.0
XXX	0	0	0	0	0.0
Multiple					
I+VIII	1	0	1	0	0.0
X+XXI	1	0	1	0	0.0
XX+XIV	1	0	1	0	0.0
II+XVI	1	0	1	0	0.0
I+XV	1	0	1	0	0.0
III+VIII	1	0	1	0	0.0
XV+XXIII	1	0	1	0	0.0
Total typed	105	5	94	11	
Not typed	37	0	36	1	
TOTAL	142	5	130	12	8.4%

The remaining series of 142 cases of pneumococcus pneumonia treated by sulfapyridine is analyzed as follows:

Table 9 shows the type incidence combined with the incidence of bacteremia and the mortality rate. The significant points are the relatively large number of cases of Type III, there being 25 such cases with three instances of bacteremia and four deaths. Two of the deaths were in bacteremia cases and two of the cases which died did not show bacteremia. This gives a mortality rate of Type III cases treated by sulfapyridine of 16 per cent, which is comparable to other reports. It is also interesting to note that in this group there were seven cases where multiple types occurred but where there were no deaths.

Table 10 shows the relationship of age groups of patients; the bacteremia incidence and the mortality rate. There were three deaths in the age group under two years; one of these deaths was in a girl three months of age with a pneumonia of Type XIII with complicating pyo-pneumothorax and bilateral otitis media. This patient had not been seen before the fifth day of the disease. The second patient was a child just under two years with a Type V pneumonia and a positive blood culture, seen first on the sixth day of disease. The third case was a three weeks old infant in which no typing was secured. Treatment was instituted after the fourth day of disease with death on the third day of drug therapy. There were no deaths in the age group between 2 and 40 years of age. There was a total mortality rate of 8.4 per cent. A significant point is that in this group 98 cases were treated within five days of onset and thus, theoretically, received adequate treatment; nevertheless two of these patients died. The majority of deaths occurred in patients seen for the first time on the fifth day or later.

TABLE X  
Sulfapyridine Treated Cases—Age—Day of Disease—Mortality Rate

Age	No. Cases	Bacteremia	Recovered	Died	Mortality Rate
0-2	27	0	24	3	7.3
2-10	26	1	26	0	0.0
11-20	18	0	18	0	0.0
21-30	8	0	8	0	0.0
31-40	17	0	17	0	0.0
41-50	9	1 (died)	8	1	11.1
51-60	13	2 (died)	9	4	30.9
61-70	13	1	13	0	0.0
71-	11	0	7	4	36.3
Total	142	5	130	12	8.4%

Treated within 96 hrs. —98 cases—2 deaths  
Treated later than 96 hrs.—44 cases—10 deaths

#### INCIDENCE OF COMPLICATIONS

Of the 142 cases treated with sulfapyridine, eight had complications caused by pneumococci. Four were empyema; four were otitis media. There was one death among the four with empyema. Three cases had arteriosclerotic heart disease with decompensation; one of these died. An-

other patient who died had periods of auricular fibrillation. There were seven patients who had more than one type of pneumococcus in the sputum, none of whom died.

#### ADMINISTRATION OF SULFAPYRIDINE

Sulfapyridine was given according to age and weight of the patient. In general, however, all adults without renal or hepatic complications were given 1 gram every hour for the first four hours, then 1 gram every four hours night and day until the temperature had remained normal or not above 100.5° F., or 38° C. for at least two days. Rarely was it necessary to exceed a total of 30 grams for adults.

We gave 0.15 gram every four hours to infants under three months of age; 0.3 gram to those six months to one year of age; and the same every three hours to those one to two years old; 0.6 gram every four hours for five year olds and 0.9 gram every four hours in the 12 year age group. The rule of giving 0.1 gram per kilo of body weight may result in too small a dose for children and infants. Crushing the tablets and administering them in a mixture of apple sauce, syrup or in gelatin capsules is useful at times.

The daily dose necessary to effect a concentration of 5 to 10 mg. per cent varies for different individuals. There is a marked variability in the absorption of the drug in different persons. The above level was found satisfactory but the effective level, as judged by the concentration in the blood, varies.

The precaution observed in the use of sulfanilamide, of not simultaneously giving magnesium sulfate, was likewise exercised here. Very seldom was it necessary to give methylene blue, but when given, the intravenous route was used because it seemed to cause less nausea than the oral administration.

Attention should be called to the need for careful observation of the blood counts, and of the urine, both during and several days after administering sulfapyridine. If gross hematuria, "stones" of sulfapyridine or severe decrease in number of blood cells of either variety, occurs, sulfapyridine should be discontinued and liberal amounts of fluid given by mouth or as 5 per cent glucose in saline by vein.

#### TOXIC MANIFESTATIONS

Two patients had "drug fever," one of these had a rash which disappeared when the drug was discontinued. There were three cases exhibiting a patchy erythema due to sulfapyridine. The occurrence of microscopic hematuria was rather frequent. No cases of gross hematuria were seen and no cases of proved renal calculi, due to sulfapyridine, were observed. It may be significant that no attempt was made to concentrate the drug in the serum by limiting fluid, but on the other hand, fluids were forced to a total of 3 to 5 liters per day in all drug treated cases. Due to the fact that in

two cases the plasma non-protein nitrogen rose after sulfapyridine therapy, the drug was not used in elderly patients showing evidence of marked renal damage. One case of Friedländer's pneumonia (not included in the series) developed jaundice one month subsequent to three weeks of sulfapyridine therapy (6 grams daily for two weeks and 3 grams daily for one week). All gastrointestinal and genito-urinary and gall bladder examinations were negative. Recovery from the jaundice was slow but complete.

In two patients of this series the erythrocyte count dropped by 1,000,000 cells in 24 hours, so the drug was discontinued. The patients recovered. There was no jaundice or untoward reaction. No case of agranulocytosis was encountered. In 48 per cent of the patients nausea and vomiting incident to the administration of sulfapyridine occurred. If the vomiting became too severe and interfered with nutrition the drug was discontinued, or in a few cases the sodium salt was given by rectum. Many times the administration of the drug, crushed and mixed with food or placed in capsules was followed by improvement in the nausea. The parenteral use of normal saline solution did not help the nausea greatly. Others have found the use of oxygen inhalation, especially 100 per cent oxygen, helpful in relieving nausea due to sulfapyridine.

Of the 130 drug treated cases that recovered the temperature dropped to normal in 74 patients within 24 hours and in 93 of the patients the temperature was normal within 48 hours.

## DISCUSSION

Due to a number of factors the serum treated series and the drug treated series are not comparable. No Type III patients received serum. There was a much larger percentage of infants and young people in the drug treated cases than in the serum treated cases. The series of drug treated cases contained a relatively small number of Types I, II, V, VII, VIII and XIV. Certain points, however, seem to be significant: (1) In the serum treated cases there were no deaths in the small groups of Types VII and VIII although the percentage of bacteremia in these groups was 15.3 per cent for Type VII and 5.2 per cent for Type VIII. In the drug treated cases there was one death each in Type VII and in Type VIII, neither of which disclosed a bacteremia. (2) In both series the highest mortality rate was in the individuals over 40 years with the secondary peak of mortality in the drug treated cases in those under two years of age. (3) In the serum treated series there were no deaths among the patients seen for the first time before the fifth day. In the drug treated series there were two deaths when the patients were seen early enough in the disease to receive, theoretically, adequate treatment. (4) Ninety-four or 81 per cent of the 116 serum treated cases recovered by prompt crisis, whereas, only 74 of the 130 patients, or 56.9 per cent of those who recovered in the drug treated group had a drop in temperature to normal within 24 hours. Pertinent in this connection is

the observation that after the crisis in the serum treated cases, the patient was practically well, clinically, whereas in the drug treated cases the patient was still very sick for several days after defervescence of temperature and frequently required continuous administration of oxygen.

Although an effort was made to maintain a blood concentration of 5 to 10 mg. per cent of the drug, it is interesting to note that the majority of the patients who recovered did so within the first 24 to 48 hours with the concentration in the blood varying between 2 to 16 mg. per cent in different cases.

### CONCLUSIONS

1. The specific rabbit anti-pneumococcus serum appears to be a very effective form of treatment for pneumonia caused by pneumococci of Types I, II, V, VII, VIII and XIV.
2. Sulfapyridine is of great value in the treatment of pneumococcal pneumonia, and, particularly with the Type III organism against which specific serum therapy has not been markedly effective.
3. Sulfapyridine is of value in the treatment of pneumococcal pneumonia where for one reason or another typing cannot be performed or where type specific serum cannot be secured. It is also of value in selected cases when combined with serum therapy.
4. Regardless of the method of treatment, the age group of the patients bears a very definite relationship to the mortality rate.
5. Regardless of the method of treatment, the day of disease upon which treatment is instituted bears a very definite relationship to the mortality rate.



# STUDIES IN PERIPHERAL VASCULAR DISEASE

## I. INTRAVENOUS CALCIUM IN OCCLUSIVE VASCULAR DISEASE\*

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THE use of calcium in obliterative vascular diseases is not a radically new departure. Its use in these conditions, by the venous route, has not to my knowledge been previously reported. Bernheim and London<sup>4</sup> have administered calcium orally in some cases and have reported some success in spastic conditions. The mode of action has, however, not been adequately explained.

In order to reduce to a minimum the amount of fluid used in saline therapy of obliterative arterial diseases, calcium gluconate was employed, in 10 per cent solution, in amounts of either 10 or 20 cubic centimeters. This was substituted for the 300 cubic centimeters of 5 per cent sodium chloride solution commonly used in some clinics for peripheral arterial disease. The idea was to find out, if possible, whether a salt, per se, exercised the main effect or whether a relatively large amount of fluid played any important part in the results obtained. A report on this point will be made in the near future.

Calcium salts were injected intravenously in a number of cases. In 30 of these recordings were made, with the Tycos recording oscillometer, of pulse amplitude before and after injection. In other cases, observations were made with the Pachon-Boullite oscillometer. Both instruments showed an appreciable augmentation of the pulse amplitude in a considerable number of cases.

The most striking phenomena, however, were clinical. Most noteworthy were relief from pain and increased ability on the part of the patients to walk. This needed explanation.

Following the intravenous injection of calcium salts, there is a generalized flush and sensation of heat, starting usually in the throat, and spreading gradually all over the body. This occurs in normal persons as well as in those with impaired peripheral circulation. No rise in blood pressure is observed. With considerable constancy, a drop is noted in both systolic and diastolic levels, more marked in the diastolic as a rule. This fall in blood pressure has also been observed by others.<sup>9, 20, 28, 30</sup> There is also, quite constantly, a slowing of the pulse rate. Nausea occurs occasionally. The extreme thirst which follows infusion of hypertonic saline solutions is not

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present after calcium injections. This would indicate that tissue fluids are not suddenly withdrawn from the tissues in order to dilute to isotonicity the excess salt, thereby rapidly increasing the blood volume. If the blood volume is not increased, how are we to account for what seems to be increased circulation? There must be some specific action of the calcium ion, and this action would seem to be essentially vasodilator.

Little has been written concerning the action of calcium on blood vessels. There is considerable published work on the cardiac action which has been admirably summarized by Berliner.<sup>2</sup> There is some disagreement, but the bulk of evidence seems to bear out the contention that calcium acts as a vasodilator. The effect of calcium on the autonomic nervous system is also not yet finally established. The effect of calcium on smooth muscle has been observed to be antispasmodic. These three factors evidently play some part in the mechanism of the findings previously mentioned. Which action is dominant, or what their interrelation may be, is not yet clear. Let us evaluate them separately and then try to correlate them in regard to their concerted action *in vivo*.

The general flush and the feeling of warmth after the infusion of calcium salts lead one to believe that superficial vessels are being dilated. How else does the skin become red and hot? This impression is strengthened by the sensation of heat in an extremity which had previously been cold for months or years because of deficient circulation. This view is shared by Sollman,<sup>35</sup> Zondek,<sup>43</sup> and Hunter.<sup>17</sup> Major and Stephenson<sup>24</sup> point out that the administration of calcium salts reduces the hypertension induced by methylguanidin. They ascribe a vasodilator action to calcium. Mancke<sup>25</sup> explains increased heart action after the administration of calcium as due to coronary dilatation, with increased flow of blood to the heart muscle. Hochrein<sup>16</sup> observed the dilator action of calcium on coronary vessels even after complete denervation of the heart. Schmidt<sup>47</sup> found that perfusion with calcium salts induced a vasodilatation in the frog, cat and rat. The flow, measured by drops per minute, increased 11 to 50 per cent over the normal rate.

Figure 1 is an oscillometric record obtained in a man with long established thromboangiitis obliterans. It will be observed that pulsation before injection is small. After injection of 2 gm. of calcium gluconate, pulsation is definitely increased. Ten minutes later the pulsation is still larger, and after 20 minutes it is about three times the original amplitude. This does not mean that the actual blood flow has increased in exactly that proportion. Mechanical factors of error in the recording apparatus are, no doubt, responsible for some distortion. But the fact remains that a distinct increase in pulse amplitude is recorded.

Figure 2 is a similar record from a man well over 60, with advanced arteriosclerosis. A similar result is apparent in this instance, but to a lesser degree. This is explained by the relatively smaller development of collateral

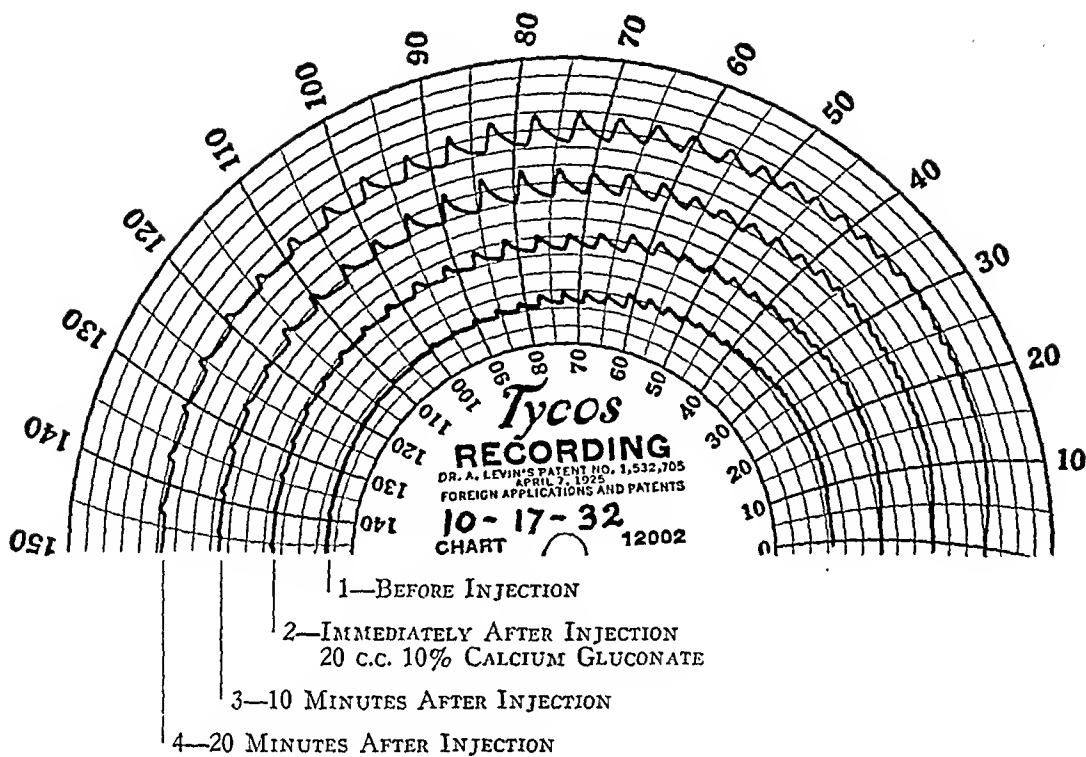


FIG. 1.

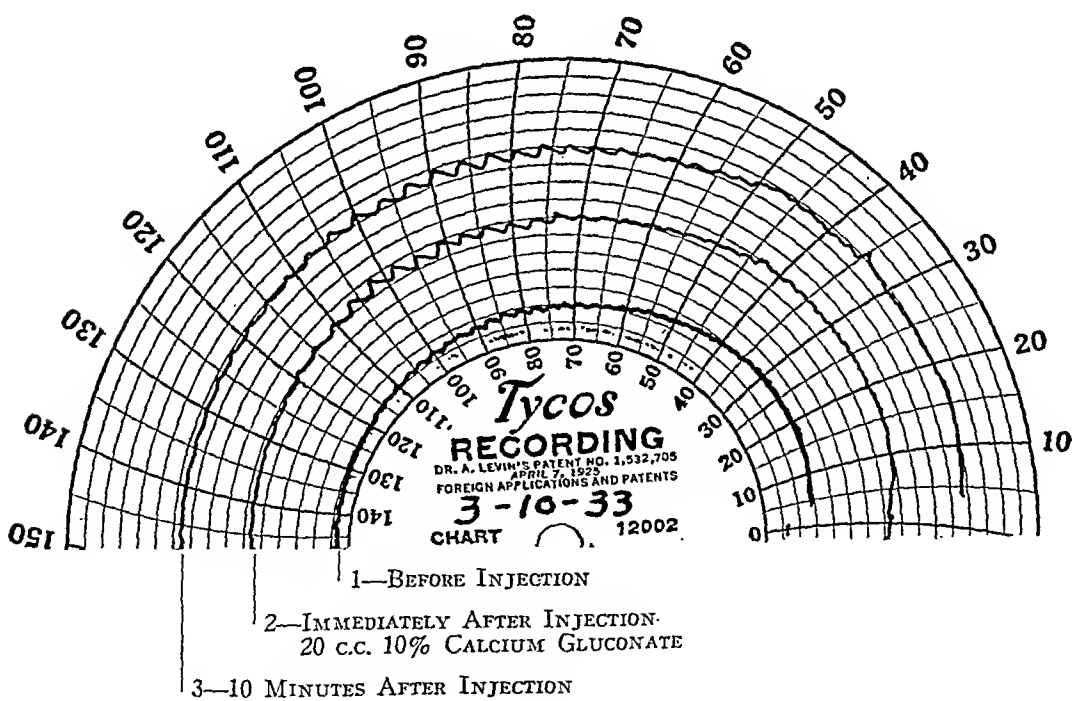


FIG. 2.

circulation in arteriosclerosis than in thromboangiitis obliterans. Of this, more later.

These records are fairly characteristic of the response regularly elicited. The others are similar. A few cases show no demonstrable evidence of this response. But, despite the absence of demonstrable evidence of increased pulse amplitude, patients get relief after injection of calcium salts. This can be explained as due to the dilatation of the collateral bed of small, nonpulsating vessels which can neither be felt nor measured but which do, in their dilated state, bring more blood to previously ischemic tissues. From the foregoing evidence, it may be presumed that calcium salts act as vasodilators.

There is some disagreement in the literature as to whether calcium stimulates the sympathetic or the parasympathetic. The observations recorded above tend to support the latter view. The analogy between calcium effects and vagus effects on heart rate and contractions is striking. Wolffe and Bellet<sup>41</sup> observed cessation of auricular paroxysmal tachycardia after administration of calcium salts. Stimulation of the vagus by various means will also stop these attacks. The inference is obvious. Billigheimer<sup>5</sup> observed that calcium stops adrenalin tachycardia immediately, but, when the tachycardia is produced by vagus paralysis with atropin, calcium has no effect. If this be so, it is logical to assume that calcium acts in this instance by vagus stimulation, a parasympathetic phenomenon. Petzetakis<sup>29</sup> also observed that calcium increases vagus irritability and that it stops extrasystoles and attacks of tachycardia. Stimulation of the vagus slows the heart. Bradycardia after infusion of calcium has been repeatedly observed by myself and by many others.<sup>8, 46, 39, 20, 9, 6, 7, 44</sup> Seekles, Sjollesma and van der Kaay<sup>33</sup> interpreted this bradycardia as a vagotonic manifestation. Edwards and Page<sup>12</sup> observed bradycardia after parathormone which induces a hypercalcemia. Hueper<sup>48</sup> observed that when parathyroid extract was given in sufficient amount to raise the blood calcium to 15 mg. per cent, marked diuresis occurred and that blood vessels, especially glomerular capillaries, were extremely distended with blood. All these facts point to a direct parasympathetic stimulation by the calcium ion or else to a parasympatheticomimetic function, through some other means, via the calcium ion. The component parts of the autonomic system being largely antagonistic, it would thus appear that calcium plays an antisympathetic rôle.

Sympathetic fibers to the extremities have been demonstrated by Kramer and Todd,<sup>19</sup> Woollard and Norrish,<sup>42</sup> Moore, Williams and Singleton.<sup>27</sup> Woollard<sup>49</sup> states: "Vasoconstriction is a continuous and tonic effect of the sympathetic system." . . . "The tonic constrictor supply by the sympathetic is the only continuous active pressor system that is known . . . something like 50 per cent of the normal blood pressure is dependent on these pressor impulses." Again: "These pressor influences pervade the entire body with the possible exceptions of the heart . . . the brain . . . and the lungs." Also: "Vasodilators include some special nerves, the chorda tympani, the cranial

parasympathetic in general, the pelvic nerves, the sacral parasympathetic . . . and finally, there is some evidence in most parts of the body of some vasodilators which belong to the gray rami of the sympathetic. These, however, are overshadowed by the vasoconstrictor fibers present in these same rami." Finally, the reports, too numerous to mention, of the results of sympathetic ganglionectomy, bear out the vasoconstrictor effect of the sympathetic system.

This leads logically to the question: "Could not the calcium effect in this instance be the result of inhibition of the neuromuscular junction between the sympathetic fibers and the smooth muscle of the arterial wall?" The inhibitory action of calcium on neuromuscular junctions has been observed by many.<sup>43, 5, 29, 37, 38, 17, 24</sup> If this action is unselectively applicable to all neuromuscular junctions, without specific predilection for any particular group or type of fibers, the matter readily resolves itself into a quantitative determination of the number of sympathetic and parasympathetic fibers in any given area. Since at least the preponderant innervation of blood vessels is sympathetic-constrictor, an inhibitory effect on these nerve endings should produce vasodilatation.

The antispasmodic action of calcium on smooth muscle is well known. Bauer, Salter and Aub<sup>1</sup> find that infusion of calcium immediately relieves the pain of biliary and ureteral colic. Sollman<sup>36</sup> describes the arrest of intestinal peristalsis as one of the toxic effects of intravenous calcium administration. The antispasmodic effect of calcium in lead colic has also been observed by Hunter.<sup>17</sup> Kennedy<sup>18</sup> gives experimental evidence to prove that calcium excess in perfusing fluid causes a loss of tone in smooth muscle. Now, since the tonic pressor innervation of the arterial smooth muscle is preponderantly sympathetic, these facts seem further to prove the antisymphathetic action of calcium.

If the vasodilator function of calcium is accepted, its value as a therapeutic agent in occlusive vascular disease is still open to question. It is not rational to believe that any substance can actually dilate an occluded vessel. The important consideration is the effect on the collateral circulation. Buerger<sup>10</sup> has called attention to the formation of collaterals in thromboangiitis obliterans. Meleney and Miller<sup>26</sup> and Lewis and Reichert<sup>21</sup> have demonstrated arteriographically that the collateral development in thromboangiitis is much greater than in arteriosclerosis. The problem involved in treating peripheral vascular occlusions is to foster the development of collateral circulation adequate to maintain nutrition of the parts more rapidly than the occlusive process can extend. By this means, the clinical condition should improve, or should, at the very least, get no worse. Clinical improvement has, so far, indicated the usefulness of calcium salts for this purpose.

Lieberman<sup>23</sup> warns of intravascular thrombosis after injection of calcium. He used toxic doses, much larger proportionately than can be tolerated in treatment. Two grams of a calcium salt is not a toxic dose, prop-

erly given. I have not seen either thrombosis or severe toxic response in many thousands of injections, other than the flush or a slight nausea.

Clinically, the salient results have been relief from pain and increased ability to walk. At first, relief from pain lasts about 24 hours, later becoming semipermanent as treatment is continued. Night cramps and rest pain have been consistently relieved. Previously cold extremities become warm again. Patients generally return of their own volition for treatment after the first course is over. They soon get to know when they need further help. It is not uncommon for patients to remain relieved for as much as two years at a time.

Earlier in this work, calcium gluconate was used. Ten or 20 c.c. (one or two grams) of a 10 per cent solution were injected slowly enough to produce only a mild flush. Rapid injection causes unpleasantly great heat, bradycardia and nausea. Very rapid injection may cause syncope. Haste is not advisable. Since this syringe technic is tedious, and because of the relative expense and instability of the older gluconate solutions, calcium chloride (diluted to about 1 or 2 per cent to prevent intravascular irritation) was tried with very satisfactory results.

The method now used is to add to an infusion of normal saline the required amount of a 50 per cent stock sterile solution of calcium chloride. This is done after the injection is started with the normal saline to be sure that venepuncture is clean. A 300 c.c. Pyrex salvarsan tube is used, and glass Luer slip connectors show by reflux of blood when the vein has been entered. The method is cheap, safe, easy to use, and offers fair protection against perivenous infiltrations due to faulty vein puncture. The few infiltrations that have occurred have not caused any appreciable damage or discomfort. The method is so simple as to be available to the bed-patient at home as well as in hospital or office.

Because of the synergism of calcium and digitalis, no digitalized patient should ever get calcium. Death may result. Berliner<sup>2</sup> and Gold and Kwit<sup>50</sup> have commented on this aspect. It is, therefore, a rule never to accept for treatment any patient receiving digitalis. All other sources of medication are carefully investigated in order to prevent errors and possible fatalities.

For the sake of brevity, results are tabulated in the following tables. No cases of short duration are presented. Most of the cases are arteriosclerotics. All patients received two grams of calcium chloride once a week for 12-week periods. The figures indicate distance walked over level ground before claudication set in, measured by patients themselves.

Figure 3 shows claudication distances before and after treatment. Original claudication distances, one-half to five blocks, are indicated by blank spaces. Dark spaces indicate improvement over and above original distances.

Figure 4 shows the degree of improvement. Percentage improvement is obtained by adding two ciphers to the figures. All original distances were reduced to a common denominator, the blank space. Improvement is in-

licated by the dark spaces. The three high figures, 40, 52 and 60, may seem fantastic but are definitely not. They are an actual index of regular ability to walk after sufficient treatment in the respective cases. The usual run of cases shows improvement not over 10 or 12 times the original claudication distance.

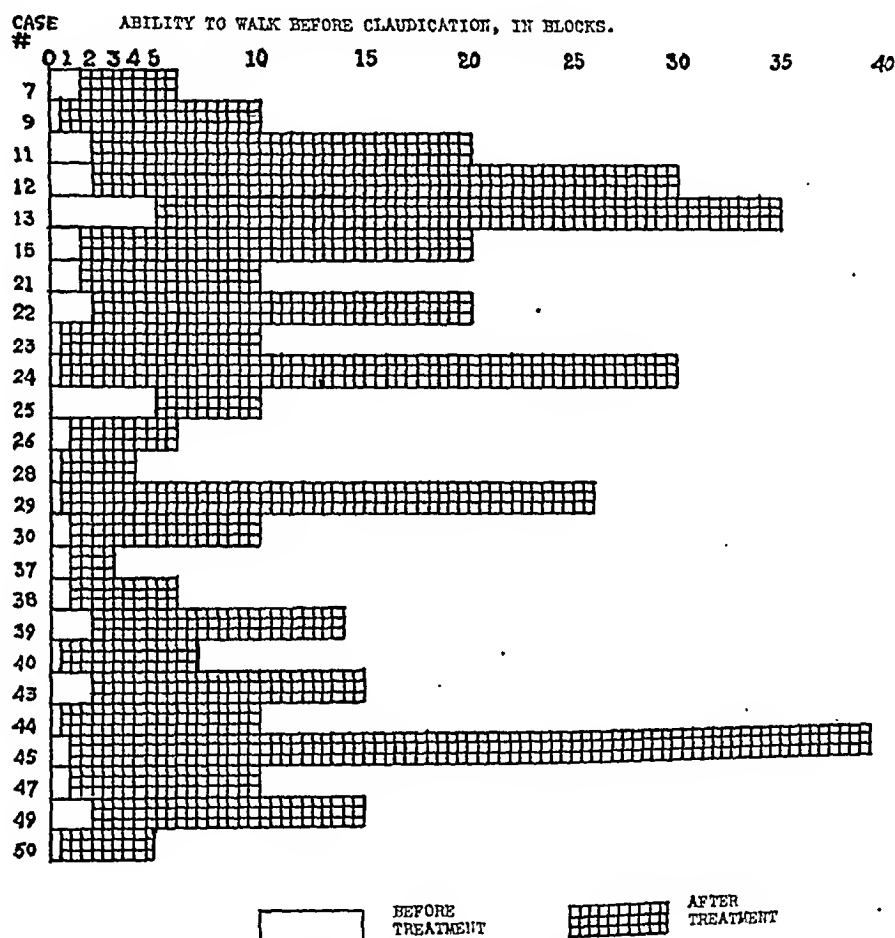


FIG. 3. Claudication distance.

Several patients showed consistent improvement in spite of gradual reduction in oscillometric readings over a period of years. This would indicate a good rate of augmentation of the collateral circulation.

#### SUMMARY AND CONCLUSIONS

It appears that the intravenous use of calcium salts, in suitable and adequate dosage, is of value in peripheral occlusive arterial diseases. The calcium effect seems to be vasodilator, on a parasympathetic or antisymphathetic basis. Claudication distance has been materially and consistently increased, rest pain and night cramps have been reduced, and ulcers have been healed with this therapy alone.

Calcium and digitalis therapy must never be mixed.

This report does not announce a panacea, nor does it in any way minimize the value of other therapeutic modalities. Rather, a form of treatment is

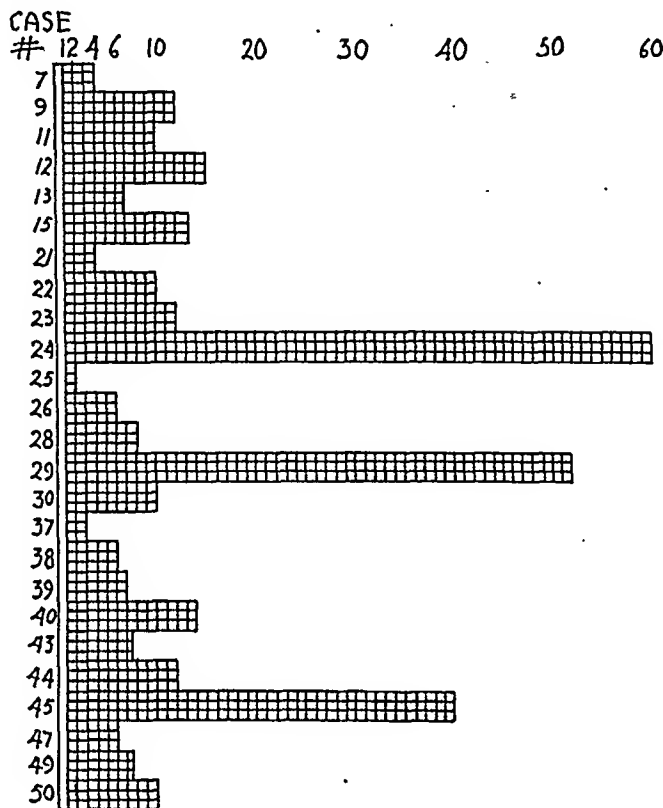


FIG. 4. Degree of improvement.

presented which is safe, cheap, simple and evidently effective. Coupling this therapy with other modalities has been found effective. It is hoped that other investigators may find the opportunity to check the method in a sufficient number of cases adequately to evaluate it.

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# INDEPENDENT VS. INTERCONNECTED TIME MARKING SYSTEM EMPLOYED IN ELECTROCARDIOGRAPHS\*

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## INTRODUCTION

IN spite of the fact that the electrocardiograph long ago attained its majority, there still appears to be a considerable amount of misunderstanding in the minds of physicians, including many who have had years of experience in the field of electrocardiography, as to what constitutes a reliable and accurate time marking system.

In interpreting an electrocardiogram, if any thought at all is given to the matter, it is usually considered that if the time marks on the tracing are uniformly and evenly spaced, they must be correct, and conversely, if they are not even or uniform in their spacing, or if their spacing varies from time to time, they are incorrect.

In many cases, the reverse is the case. An accurate time marker, entirely independent of the mechanism which drives the paper or films, will produce time marks which are entirely accurate, even though variations in the speed of the paper or film cause the spacing between the time marks to be uneven. These time intervals can be measured and interpreted with perfect confidence in their accuracy.

Conversely the non-independent "time" marker, driven from the same mechanism which drives the paper or film, will always produce "time" lines which are uniformly and evenly spaced, regardless of variations in the speed of the paper driving mechanism, and consequently of the paper. Such time marks always *look* correct, although they may be considerably in error. A prolonged P. R. interval, or an apparent arrhythmia may be due to nothing more than a variation in the speed of movement of the paper or film.

*Figure 1.* Rate—113 per minute. Tracing taken with a portable electrocardiograph which has an interconnected time marking system. The patient's clinical heart rate was 96 per minute while the tracing indicates the heart rate to be 113 per minute and a sinus arrhythmia which was not present clinically.

*Figure 1-A.* This tracing was taken of the same individual as figure 1, while deliberately varying the camera speed. The heart rate appears to vary from 112 to 150 per minute and the sinus arrhythmia is quite marked. In spite of the fact that the mechanical factors are responsible for this inaccuracy, the timing device fails to show it. The dark area in this tracing also

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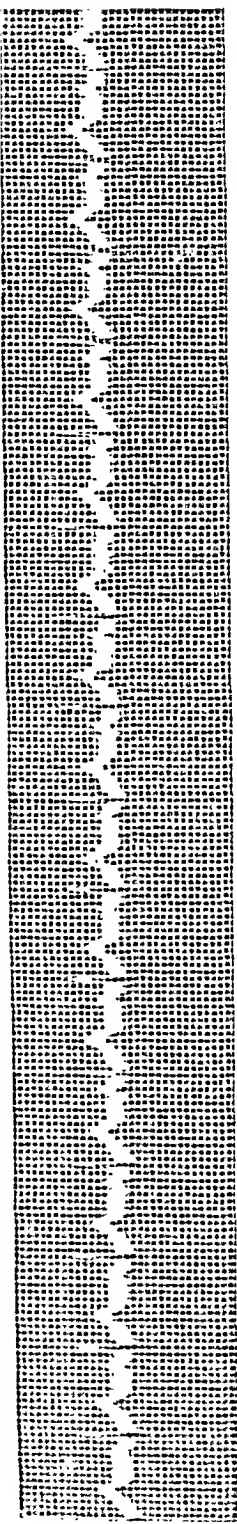


FIG. 1.

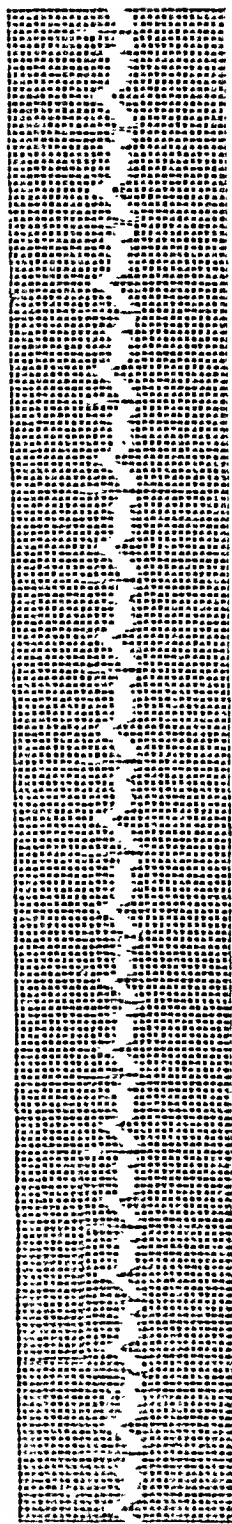


FIG. 1-A.

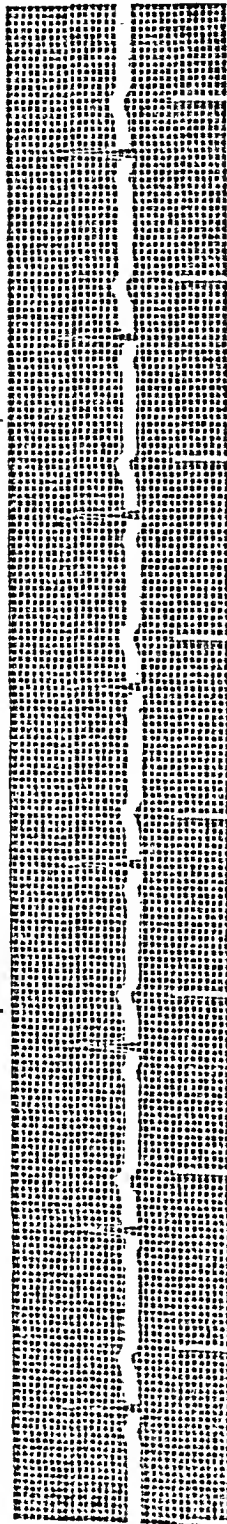


FIG. 2.

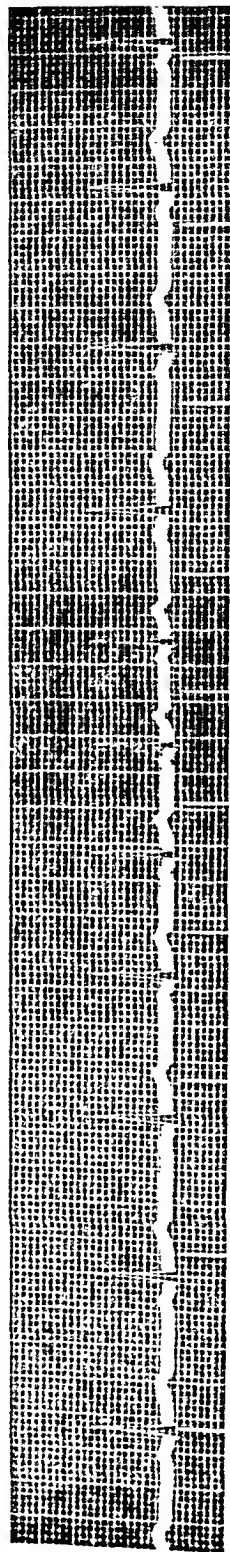


FIG. 2-A.

demonstrates the slowing of the camera without any change in the time marking.

A description of the characteristics of these two classes of time marker will make the foregoing clear.

#### INDEPENDENT TIME MARKER

The independent time marker is, as its name implies, one which operates entirely independently of the motor which drives the camera (photographic recorder). An independent time marker, to give any assurance of accuracy, must be so designed as to run in synchronism with a source of current which provides a series of impulses at a known and invariable rate. Such a series of impulses is obtainable from any well-controlled alternating current lighting circuit, from a well-adjusted electrically driven tuning fork, from a contact-making pendulum, or a contact-making clock.

Since, in electrocardiography, the universally accepted time intervals are represented by a series of marks on lines  $\frac{1}{25}$  or 0.04 second apart with every fifth line so accentuated as to represent  $\frac{1}{5}$  or 0.2 second, it is practically essential to employ a rotary form of time marker, as it is not possible with any non-rotary form to produce these accentuated lines every  $\frac{1}{5}$  second.

Accordingly, the most practical form of independent time marker consists of a small, low power, true synchronous motor, either of the solid iron, toothed rotor type (hand starting) or of the shaded-pole self-starting type. On the output shaft is mounted a wheel with five spokes, one spoke being wider than the other four. These spokes intercept the light beam which is projected by the galvanometer into the photographic recorder, each spoke, as it passes through the beam, cutting off the light, and producing a thin line across the moving strip of bromide paper or film, during the momentary dark period. The fifth extra wide spoke causes a dark period of longer duration, producing a heavier or thicker line.

By the correct choice of the number of rotor teeth in the solid iron rotor type, and the correct choice of reduction gearing in the shaded pole self-starting type, both types may be driven by, and in synchronism with, either an electrically driven tuning fork, or a commercial frequency alternating current.

Independent time markers of this nature are positive in their accuracy. The time marks which they produce in the photographic record are absolutely correct, no matter how the speed of the moving paper or film may vary.

#### NON-INDEPENDENT TIME MARKERS

A time marker is non-independent when it is interconnected with, and driven by the same source of power which drives the photographic recorder. Such time markers are still incorporated in certain types of electrocardiographs. These machines are adequate in the hands of the experienced, particularly if they have facilities to check any questionable electrocardiogram.

The main reasons for their use are: first, their cheapness; second, in the case of vacuum tube electrocardiographs, that the introduction of any device, in close proximity to the amplifier, which operates either from alternating or from intermittent direct current, will, almost inevitably, produce an objectionable amount of electrical interference in the record.

It should be perfectly obvious that in the case of a "time marker" geared to, and driven by, the same mechanism which drives the paper or film, any variation in the speed of the driving mechanism, and, in consequence, of the paper or film, must be accompanied by a corresponding and absolutely proportional variation in the speed of rotation of the "time" wheel and, consequently, the "time" marks on the tracing will *always* be exactly the same distance apart, regardless of the speed of the paper or film.

To put it another way, an interconnected "time marker" will always produce a time mark each time the paper or film has moved a definite distance. Therefore, if the time marker is so geared as to produce "time" marks one millimeter apart, which is the usual practice, these marks will always be one millimeter apart, regardless of speed, or variation in speed, of the paper or film, and regardless of the *time* required to move the paper or film a distance of one millimeter.

Once this is clearly understood, it must be equally clear that such a non-independent "time marker" is not a true time marker, but merely a *distance* marker. The marks produced by such a device, therefore, give an inaccurate and misleading time reference, unless the camera drive mechanism runs at one fixed invariable speed. Inasmuch as all spring motors, and all electric motors with the exception of the true synchronous alternating current motor, are subject to speed variations, it is impossible to assure that the paper or film shall always run at one fixed invariable speed. Although all precautions are being taken by manufacturers to assure a fixed speed, they all equip the machines with a time marking device. This is to serve as an index of speed variations, but from what we have already expressed, this device does not serve any purpose if it is not independent. If the speed of the camera did not vary and were absolutely fool-proof, which is impossible, there would be no necessity for a time marking device and additional mechanisms and expenditures. The paper could be marked when prepared or a ruler provided as a measuring device.

The solution of the problem of non-independent time markers may be synchronous alternating current motor to drive both the paper and the time marker. However, there are sufficient objections to the low-power synchronous motor to render its use, for camera drive purposes, unattractive.

Attempts have been made to insure constant speed of the camera drive, by incorporating some form of governor. The governor employed has almost always been of the friction brake type such as is used in phonographs. Such governors are not reliable, owing to the inevitable change in the character of the friction brake surfaces with continued use.

To illustrate and make clear the effects which we have discussed above,

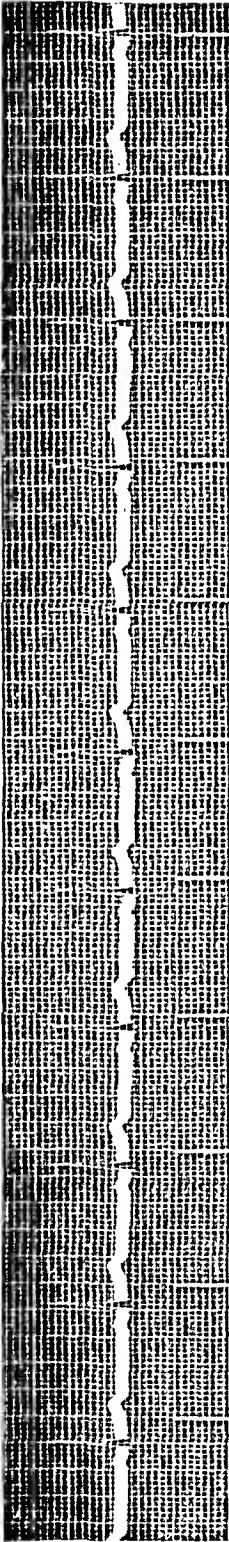


Fig. 3.

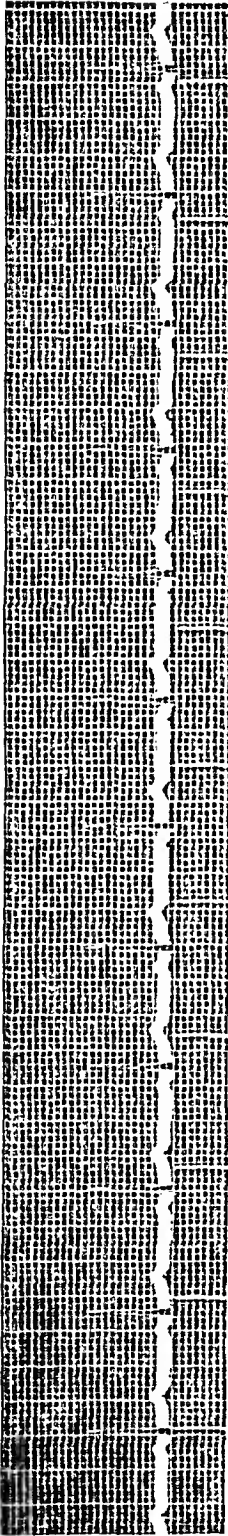


Fig. 3-4.

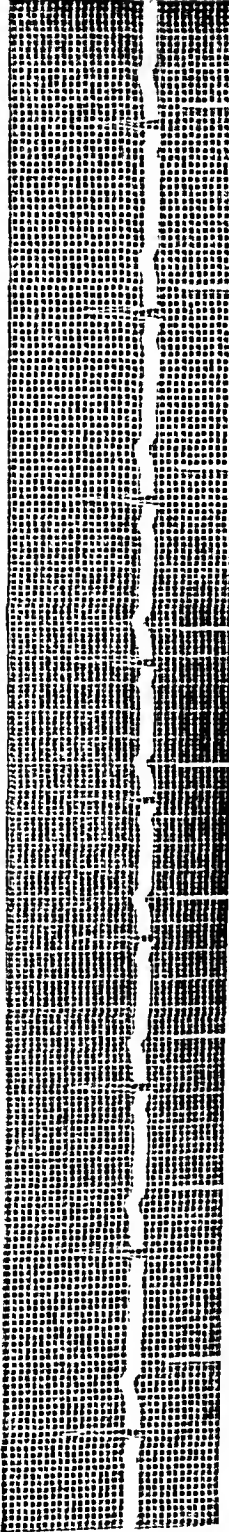


Fig. 4.

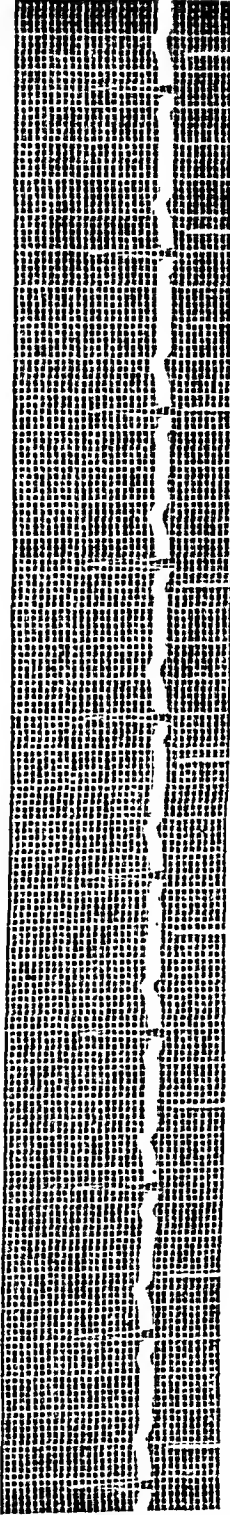


Fig. 4-4.



we show a series of tracings which illustrate clearly the errors into which the physician may be led in the interpretation of electrocardiographic tracings taken on equipments which incorporate these non-independent or interconnected time markers. These tracings were taken on two different equipments, one incorporating the recommended type of independent synchronous time marker, the other incorporating a non-independent time marker which was interconnected with and driven by the camera motor. The short marks along the lower edge of each tracing were made by an additional laboratory precision type time marker, marking accurate one second intervals.

*Figure 2.* Taken with independent time marker. Camera speed 25 mm. per second. Heart rate 61 per minute.

*Figure 2-A.* Taken with non-independent time marker. Camera speed 25 mm. per second (as nearly as it could be adjusted without a great deal of trouble). Heart rate approximately 68 per minute.

*Figure 3.* Taken with independent time marker. Camera speed 20 mm. per second, or 20 per cent slower than normal. Heart rate 59 per minute. It will be noted that although the camera was running 20 per cent slow the time marks on the tracing are still absolutely in step with the one second time intervals. In other words, the spacing between the time marks is 20 per cent less than at the normal speed of 25 mm. per second so that the timing is still absolutely correct.

*Figure 3-A.* Taken with non-independent time marker. Camera speed 20 mm. per second or 20 per cent slower than normal. In this case it will be noted that the "time" marks are spaced exactly the same distance apart as when this particular camera was running at its normal speed of 25 mm. per second (figure 2-A). Note, however, that the one second intervals which are imposed by an entirely independent time marker, are spaced considerably closer than in 2-A. The actual heart rate as measured from the correct one second time intervals is 66 per minute. However, if the heart rate is measured from the supposedly correct time marks on the tracing, the heart rate would appear to be about 86 per minute—an error of 30 per cent.

*Figure 4.* Taken with independent time marker. Speed of the camera was varied during the tracing from 19 mm. to 26 mm. per second—a change of 27 per cent. Please note that the spacing between the time lines varies in exact proportions to the speed of the camera. Note also that by measuring individual heart beats in relation to their adjacent time lines the heart rate is 59 per minute whether the time intervals are measured at the highest or at the lowest speed.

*Figure 4-A.* Taken with non-independent time marker. The camera speed was varied during the tracing from 16 mm. to 25 mm. per second—a change of 36 per cent. Note here again that the "time" lines are still spaced exactly the same distance apart as when this camera was running at 25 mm. per second (figure 2-A). Note, at the same time, that the one second intervals vary in their spacing with the camera speed. The equal spacing of the time lines in spite of the variation in speed of the camera gives



the effect of fairly pronounced arrhythmia. By measuring individual beats from their adjacent time lines the heart rate appears to vary from 65 to 103. However, if we measure the individual beats with relation to the adjacent independent one second time intervals, we find that the heart rate is approximately 66 per minute no matter where it is measured on the tracing.

#### SUMMARY

The foregoing demonstrates that in any photographic recording system such as that of an electrocardiograph, the only reliable and accurate time marker is one which is driven entirely independently from the camera driving system, by alternating current of controlled frequency or by intermittent direct current impulses provided by a tuning fork or similar device.

It also demonstrates that the so-called time markers which are connected to, and driven by, the same source of power which drives the camera are often unreliable and may be misleading since reliance can be placed in them only if they are checked and if necessary adjusted before and after each tracing is taken.

While interpreting an electrocardiogram it is important to investigate the type of instrument used. Should it reveal any abnormalities which may result from mechanical defects, the electrocardiogram should be checked with an instrument so scientifically and accurately constructed that mechanical irregularities can be recognized by means of a proper timing device.

The manufacturers of the less expensive instruments have made a fine contribution in making instruments available to a greater number of physicians. Improvement of the timing device will greatly enhance their value.

# THROMBOSIS OF THE ABDOMINAL AORTA; A REPORT OF FOUR CASES SHOWING THE VARIABILITY OF SYMPTOMS \*

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THROMBOSIS of the aorta, an uncommon and serious condition, has been recognized since Graham's description in 1814. Occasional cases were subsequently reported, so that Welch<sup>1</sup> was able to collect 59 cases of thrombosis and embolism in 1898. The number had increased to 94 in 1922<sup>2</sup> and Banovitch and Ira<sup>3</sup> in their summary of the literature cited 105 cases in 1928. Since then a number of cases have been reported yearly.

A majority of the reported cases were associated with chronic arterial and cardiac diseases. Many of them followed mitral stenosis and auricular fibrillation. The location of the thrombus varied, but the distal portion of the abdominal aorta was the most common site. Thrombi above the origin of the superior mesenteric artery were rare, while those near the bifurcation commonly extended into the iliac, femoral, popliteal or even the posterior tibial arteries—the so-called riding or straddling thrombi.

The usual symptoms described were those arising from a thrombus at or near the bifurcation of the iliac arteries. Severe to agonizing pain that arose in the loins and extended down both legs was the outstanding feature and indicated a rapidly forming thrombus. Intermittent claudication was said to be a common early sign in slowly forming obstruction; numbness, formication, pallor, coldness, areas of anesthesia on the legs or thighs, paraplegia and finally gangrene often followed. Either one or both lower extremities were involved. The type and extent of gangrene was dependent upon the speed and completeness of arterial closure and the inadequacy of collateral circulation. Diminution of pulsation of the larger arteries of the lower extremities was stressed as an important diagnostic sign.

The flexible symptomatology of the condition is well illustrated by the following cases. Case 1 was selected from private practise. Cases 2 and 3 were kindly supplied by Drs. H. O. Weishaar and Don C. Sutton, respectively, while Case 4 was taken from the records of the Research and Educational Hospital.

## REPORT OF CASES

### THROMBOSIS SECONDARY TO A RHEUMATIC CARDITIS

*Case 1.* M. B., a white man, aged 45, complained of swollen joints and palpitation when first seen on February 5, 1935. As a boy of 10 he had a single attack of rheumatic fever that lasted for a month. It apparently left no traces but early in 1917 mitral stenosis was discovered. In 1923 he first experienced gradually increasing weakness and fatigue. He went to a clinic where he had his tonsils removed. Six

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weeks after the operation his hands and knees became acutely swollen and tender. This bout of polyarticular rheumatic fever lasted 10 months, involved most of the joints of the body and there was considerable residual deformity. It necessitated eight months further bed rest. In January 1925 he had several fainting attacks followed by signs of decompensation. An examination at that time disclosed a high grade mitral stenosis, aortic insufficiency, aortic stenosis, auricular fibrillation and rheumatic polyarthritis. After a short stay in the hospital and rapid digitalization he went home much improved. Slight benefit followed the administration of an especially prepared streptococcus vaccine. An autogenous vaccine was then used. The arthritis improved so that he was able to get out of bed and walk about. By July he spent much of his time out-of-doors walking about without discomfort.

That summer he called attention to a sharp cramp-like pain in his upper abdomen, associated with considerable belching and some nausea. He referred to it as "a burning in my solar plexus." A digitalis intoxication was not excluded despite the fact that none of the other toxic effects were present. Nevertheless, the drug was discontinued. During the next three days the pain slowly disappeared. It permitted him gradually to resume his former activities. Tonic doses of digitalis, 0.06-0.18 gm. (gr. 1-3) enabled him to carry on some of his business. On two occasions large doses of digitalis were given in an attempt to reproduce the abdominal pain. The pain could not be duplicated. A bradycardia of 60 to 64 beats per minute was the only effect.

On November 3, 1935, there was a second attack of acute abdominal pain. It was dull, heavy, cramp-like in character and definitely limited to the upper abdomen. There were no exertional, emotional or gastric antecedents. An irregular pulse rate of 115-120 beats per minute was noted. In addition to the previous cardiac findings there was an enlarged liver. The next morning the patient was considerably relieved by the belching of gas. By evening the pain was severe and colicky, associated with persistent nausea. The pain was then localized just above the umbilicus involving an area 5 cm. in diameter. Tenderness and rigidity soon appeared in this area. Large doses of dilaudid 0.003-0.009 gm. (gr.  $\frac{1}{20}$ - $\frac{3}{20}$ ) and morphine sulfate 0.016-0.032 gm. (gr.  $\frac{1}{4}$ - $\frac{1}{2}$ ) failed to relieve the pain. On the third day the rigidity extended down to the umbilicus. He vomited a small amount of bile-stained mucus. The blood pressure fell to 85 systolic and 60 diastolic. Both legs felt warm to touch and the cyanosis of the toes was no greater than that of the finger nails. Slight edema was present over the right tibia. At no time were there areas of paresthesia or anesthesia over the legs, thighs, or pelvis nor did the patient complain of any pain in these structures. He grew progressively worse, went into coma, and died on the fourth day of this illness.

Autopsy revealed an enlarged heart that weighed about 500 gm. The pericardial sac contained about 200 c.c. of clear fluid. Several easily ruptured adhesions were attached to the anterior surface of the right ventricle, conus arteriosus and pulmonary artery. The left atrium was greatly dilated. The auricular appendage was filled with firm red and red-brown thrombi which were attached to the wall between the trabeculae. Small irregular stripes and spots of yellow pigment were visible through the endocardium of the right side of the interventricular septum. The maximal thickness of left ventricular wall was 1.5 cm. The mitral valve barely admitted the tips of two fingers and measured 28 mm. Its superior surface was smooth, the leaflets showed definite fibrous thickening and along its margins were a few fine pink-yellow granules. The aortic valve showed great thickening of all three cusps, complete fusion and calcification of the anterior cusps and several fine granules along the line of closure adjacent to the commissures.

Extensive atheromatous degeneration of the thoracic aorta was present. At least 90 per cent of the intimal surface was covered by slightly elevated yellow plaques. Below the diaphragm many of these plaques were softened and ulcerated. Yellowish mushy substance was scraped from their surfaces. Firmly attached friable

thrombi forming thick polypoid masses covered the intimal surface of the aorta below the origin of the renal arteries. One of these extended for a few millimeters into the orifice of the right common iliac artery. Patches of fatty degeneration and small mural thrombi were seen in the first few centimeters of the left common iliac, but there was no appreciable obstruction of either iliac artery.

No noteworthy changes were found in the other organs of the body.

#### DISLOCATION OF A MURAL THROMBUS FROM AN ANEURYSM OF THE ABDOMINAL AORTA

*Case 2.* L. E. B., a male, aged 80 years, was admitted to the Evanston hospital on December 9, 1930, and died on December 17, 1930. He had retired from business 10 years previously. Four days before admission he had a dull pain in the epigastrium followed, the next day, by a sudden excruciating pain in the left upper quadrant. Large doses of morphine sulfate, 0.016 gm. (gr.  $\frac{1}{4}$ ) gave some relief from the pain. He was sent to the hospital where an examination revealed tenderness in the upper abdomen. A pulsatile mass the size of a grapefruit was found in the left hypochondriac region. Blood pressure was 132 systolic and 90 diastolic. Roentgenologic studies suggested an extrinsic cystic tumor pressing on the gastrointestinal tract. Five days after admission the pain in the left upper quadrant again was suddenly intensified. Nausea, vomiting and rigidity followed in succession. In an attempt to establish a diagnosis an exploratory laparotomy was performed. During the exposure of the mass, which later proved to be an aneurysm, a large mural thrombus was dislodged. The patient's condition immediately became critical and he died 18 hours later.

Autopsy showed moderate hypertrophy and dilatation of the heart. On cut section there were a few small gray fibrous areas, otherwise the myocardium appeared normal.

There was a high grade atherosclerosis of the aorta, especially the abdominal portion. Just above the aortic valves, the aorta measured 90 mm. in circumference. Its wall was inelastic and showed numerous raised yellow patches in the transverse and descending portions of the arch. These involved 60 per cent of the thoracic aorta and the thickenings were grouped about the orifices of the intercostal arteries. Some plaques were calcified. One shallow ulcer was present in the lower thoracic region.

The abdominal aorta was enlarged by a fusiform aneurysm that filled the left half of the abdomen. From a point opposite the renal arteries to the aortic bifurcation, the aneurysm had completely destroyed most of the posterior wall of the vessel. Within, the aneurysm was lined by a thick layer of lamellated blood clot. At the distal end of the enlargement near the bifurcation of the common iliac arteries there was a soft, granular thrombus that partially occluded the abdominal aorta. The muscular and fatty tissue surrounding the aneurysm contained large amounts of dark clotted blood. A large hematoma completely encased the left kidney.

#### THROMBOSIS FROM AN IMPAIRED CIRCULATION IN AN ATHEROSCLEROTIC ARTERY

*Case 3.* M. E. B., a woman, aged 71 years, entered the Evanston hospital badly decompensated. There was a history of arthritis during the past seven years which caused difficulty in locomotion. She had had hypertension for many years. Three years prior to entrance there had been the first break in cardiac compensation. After a month's stay in the hospital she had improved so that she was discharged. Another lapse in compensation necessitated her return to the hospital on October 11, 1930. The only other change in her condition from that at the first admission was a fall in systolic blood pressure from 238 to 186; the diastolic pressure remained 126 mm.

A week after entrance she had considerable abdominal pain and severe nocturnal dyspnea. For the next few days there was a diarrhea of four to six semi-formed

movements. No blood was found in the stools. With rest and medication she improved.

Her left leg suddenly became swollen a month after admission. The next morning the foot and leg were numb. Within a few hours they were swollen and red, then became cold, cyanotic and pulseless. There was a fever of 99.8° F., a leukocytosis of 22,000. The patient complained of severe pain in the left leg and later in the whole left side. There was a complete loss of tactile perception over the leg and extending along the inner side of the thigh. Blotchy areas of cyanosis developed the next day spreading over the heels, lateral aspect of ankle, and posterior surface of the left foot; gangrene followed that evening, advancing to the knee. The patient lapsed into coma and was spared the agonizing pain in the extremities. Similar bluish-pink to plum colored discolorations developed over the right ankle later that evening. They advanced involving the knee, thigh and buttock in succession. Early the next morning the patient died.

Autopsy revealed a moderate enlargement and dilatation of the heart. There were parietal thrombi of the right atrium and left auricular appendage. Both lower pulmonary lobes showed recent infarcts. Atherosclerosis and calcification of the aorta were most marked in the abdominal portion. Beginning at a point just below the inferior mesenteric arteries the abdominal aorta was completely closed by a thrombus which was adherent to practically the entire circumference of the wall, and extended downward into both common iliac arteries going into the internal and external branches on either side. The thrombus was softened in the portion lying between the bifurcation and a point two inches above it. The orifice of the right renal artery was partially closed by the thrombus.

#### RETROGRADE THROMBOSIS

*Case 4.* H. E., a 56 year old white male, complained of "shooting pains" in his legs and feet for five years before admission to the Research and Educational Hospital. The pain was worse when he stood for a long time or when he walked but it was relieved after a short period of rest. During the last three years these attacks of pain had increased in frequency and intensity. He noticed a small nodule on the dorsum of his left great toe in 1932. It became the seat of chronic inflammation which necessitated the amputation of the toe in December 1933. Soon afterward the lateral aspect of the left foot was infected and discharged pus intermittently for three years. A month before entrance he began to expectorate small quantities of muco-purulent sputum and experienced severe pain in his right chest. Dyspnea followed and together with the pains in his feet denied him any rest at night. On admission to the hospital he was very dyspneic, and had early gangrene of both toes with moderate edema of the ankles. Systolic blood pressure was 125, diastolic 98. There was limited excursion of the right lung, dullness and absent breath sounds. The apex beat of the heart was in the anterior axillary line and a systolic thrill and presystolic gallop rhythm were found. Both feet were reddish blue, purple and cold. Several draining sinuses clustered about the amputated stump of the left great toe. Neither the dorsalis pedis nor posterior tibial arteries could be felt, but there were weak pulsations over the popliteal artery. A roentgen examination of the left leg failed to show the arteries, but it did reveal a sclerosing periostitis of the fibula. The pain in his leg was so severe that it necessitated the almost constant use of morphine. Conservative management was tried for three weeks without avail, so a mid-thigh amputation of the left leg was performed. During this time there had been an increase in his dyspnea, and the percussion note over his right chest became flat. Clinical findings and roentgen films suggested a diagnosis of carcinoma of the right lung. Two weeks after the first amputation the right leg was removed at the upper third of the thigh. At this operation a tourniquet was not needed for the sclerotic vessels bled very little. He died 36 hours after the second amputation.

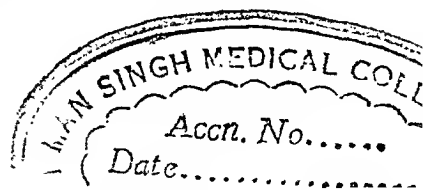
Postmortem examination disclosed a distended abdominal aorta. It contained a large thrombus at the bifurcation of the aorta, adhering to the intima of the vessel and extending into both iliac vessels. The thrombus varied considerably in consistency, the central portion being soft and the outer portions quite firm. The aorta was more adherent to the inferior vena cava than normal. A large thrombus was also found in the inferior vena cava which extended to the iliac veins, the right gluteal vein and the left femoral vein. A bronchogenic carcinoma of the right primary bronchus with metastases to the liver was also found.

### COMMENT

The clotting of blood within its own vessels during life is an alarming condition. Its causes and mechanisms have been adequately described by many. Changes in an organ or part secondary to deprivation of blood flow by a thrombus are perhaps of greater interest. Sudden cessation of blood flow in one of the larger vessels produces a symptomatology that is dependent upon the anatomy of the part, the extent of collateral circulation and the rapidity of thrombus formation.

In the past the entire symptomatology of thrombosis of the abdominal aorta has been ascribed to the stoppage of blood flow through the iliac and femoral arteries. The sharp shooting leg pains, the abolition of femoral, popliteal or posterior tibial pulsations, and the ascending gangrene of the legs were cited as supporting evidence. Welch<sup>1</sup> believed the absence of pulsation in the arteries of the lower extremity was the sign of greatest value. This sign is not, however, diagnostic as it occurs in severe anemias, arteriosclerosis and calcification of the larger arteries of the lower extremity, coarctation of the aorta, and extensive thrombophlebitis.

Coincident with the arrest of flow to the legs there are frequently ischemic changes in the spinal cord. These have not received sufficient attention. Most of the older textbooks and literature described in detail the vascular changes in the larger arteries, but scarcely mention a similar pathologic invasion of the smaller arteries, e.g., the intercostal or lumbar arteries. Ligature of the abdominal aorta below the renal arteries (Stenson's experiment) resulted in a paraplegia which was shown to follow an ischemia of the cord. These experiments have been frequently confirmed using a variety of animals. Recently, the problem has been critically re-investigated by Reichert, Rystand, and Bruck.<sup>4</sup> Ligation of one or more paired lumbar arteries in dogs, they found gave results almost identical with Stenson's experiment. Further, four patients were reported by these authors with Déjérine's syndrome, viz., intermittent claudication of the thighs, weakness of both lower extremities, and absence of neurologic signs and of syphilis, whose roentgen-rays revealed arteriosclerosis of the lower abdominal aorta. It was their opinion that the claudication resulted from ischemia of the cord due to occlusion of the spinal branches of the lumbar arteries. In fact, an ipsilateral occlusion of one or more lumbar arteries was observed in a patient who had a unilateral claudication.



A brief review of the anatomy of the lower abdominal aorta would be pertinent. Branches of the abdominal aorta are said to be segmentally arranged. It is believed that three sets of vessels arise from each segment: an anterior, lateral and posterior. The anterior set are reduced by fusion or degeneration to single vessels as the celiac, superior mesenteric and inferior mesenteric. Most of the lateral set disappear except the renal, suprarenal, and spermatic, while the posterior or third set become the paired lumbar arteries, which serve as homologues of their neighbors above, the intercostals.

The lumbar arteries arise from the posterior aspect of the aorta, wind transversely around the bodies of the vertebrae, behind the sympathetic trunk to the spaces between the transverse processes, where a large branch (*ramus dorsalis*) is given off, while the remainder of the vessel courses forward to terminate by anastomosis with other anterior abdominal arteries.<sup>5</sup> There are four branches of the lumbar arteries. A vertebral branch (*ramus vertebralis*) which sends twigs to the psoas, quadratus lumboris and oblique muscle of the abdomen. The dorsal branch (*ramus dorsalis*) which passes backward between the transverse processes to divide into three branches: a lateral that supplies the multifides; a medial that supplies the sacrospinalis muscle and a spinal which supplies the tissues of the spinal canal and the spinal cord. A fourth branch of the lumbar arteries is the renal (*ramus renalis*) which goes to the capsule of the kidney.<sup>6</sup>

It is thus evident that cessation of blood flow through the spinal branches (*rami spinalis*) of the lumbar arteries will produce the focal lesions of the spinal cord described above.<sup>7</sup> Recognition of the condition is difficult. Even though there has been much written concerning thrombosis of the larger branches of the abdominal aorta, the condition is difficult to diagnose. Trotter<sup>8</sup> in an excellent monograph on the subject remarked that superior mesenteric thrombosis was recognized before death or post mortem only 13 times in 360 patients. Inferior mesenteric thrombosis is an equally perplexing diagnosis, while the differentiation between them, "need not detain us long as it is a refinement that is not likely to be attempted in a disease that is itself difficult to recognize." Some notice has been given to thrombosis of the renal arteries but similar changes in the supra-renal, spermatic or ovarian, or lumbar arteries have scarcely been mentioned.

Thrombosis of the abdominal aorta is a relatively infrequent, though by no means a rare clinical entity. Its approximate incidence may be judged by the records of the Research and Educational Hospital, where it occurred once in 1047 post mortems. While it is true that patients are selected for admission according to their teaching value, yet in none has thrombosis of the aorta or its branches been suspected. Consequently the above ratio may be taken as a fair indication of the incidental frequency of the condition in a general hospital.

Recognition of the condition is dependent upon the rapidity and extent of arterial closure of the aorta, when the usual symptoms make its identi-

cation easy (Case 3). Less rapidly forming obstructions give a delayed symptomatology as in Case 4. A much slower process as the gradual erosion of an abdominal aneurysm may be symptomless for some time. Sudden detachment of a large mural thrombus in an aneurysmal sac may occlude the distal orifice sufficiently to give a picture of acute obstruction (Case 2). Slowly degenerative atherosclerotic changes are most difficult to recognize, and since the process is generalized thrombi are likely to occur in a variety of places throughout the vascular tree at irregular intervals. Such vascular occlusions in more peripheral vessels may confuse the picture and cause the overlooking of a thrombosis of the abdominal aorta.

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## STUDIES IN DYSTROPHIA MYOTONICA. IV. MYOTONIA: ITS NATURE AND OCCURRENCE\*

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AFTER grasping an object with great force, a normal person is occasionally conscious of a little difficulty in relaxation. Because this difficulty is slight and occurs only under unusual circumstances, it is in no way disabling and therefore scarcely noticeable. As a result of an inherited defect, other persons are unable to relax their muscles rapidly after contractions of ordinary strength. Under these conditions the muscles remain contracted for some time after the effort to contract them has ceased. Because the contraction persists during what is normally the phase of relaxation, the difficulty appears as a slowness in relaxation. This prolonged contraction or delayed relaxation is called myotonia. The duration of the contraction varies with the strength of contraction and the degree of involvement of the muscle; the stronger the contraction the more marked the myotonia. In some persons, however, a very strong contraction will result in only slight myotonia; in others, even very weak contractions are associated with marked myotonia. A minute or more may, at times, be required for the muscle to return to its resting state.

Depending on the location of the involved muscle, affected individuals show varied disabilities. Involvement of the muscles of the forearm and hand results in a difficulty in releasing objects once grasped. The carpenter may not be able to release his hammer or the brakeman the handle of the box car. Involvement of the muscles of mastication may result in the jaw remaining shut for several seconds after biting down on some firm food. Involvement of the muscles of the legs makes walking difficult. Involvement of the eye muscles may result in the eyes remaining fixed after a sudden glance to the side. When most of the muscles of the extremities are involved, a sudden movement such as results from fright, may produce a marked myotonia in both flexors and extensors and the affected individual, unable to move his limbs, falls to the ground "as a log." Although associated with a feeling of stiffness, myotonia is not painful.

Fortunately, myotonic muscles show the saving characteristic that each time the muscle is contracted the myotonia becomes less and after several contractions temporarily disappears (figure 1). Thus, although on the first bite the muscles of mastication may require many seconds for relaxation, the second bite will require less time, the third still less, and so on, until the in-

\* Read at the New Orleans meeting of the American College of Physicians March 31, 1939.

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dividual can chew his food with no evident difficulty. On starting to walk, the first few steps are difficult but the difficulty becomes less with each step until it is entirely gone. The sudden bringing into use, however, of a new

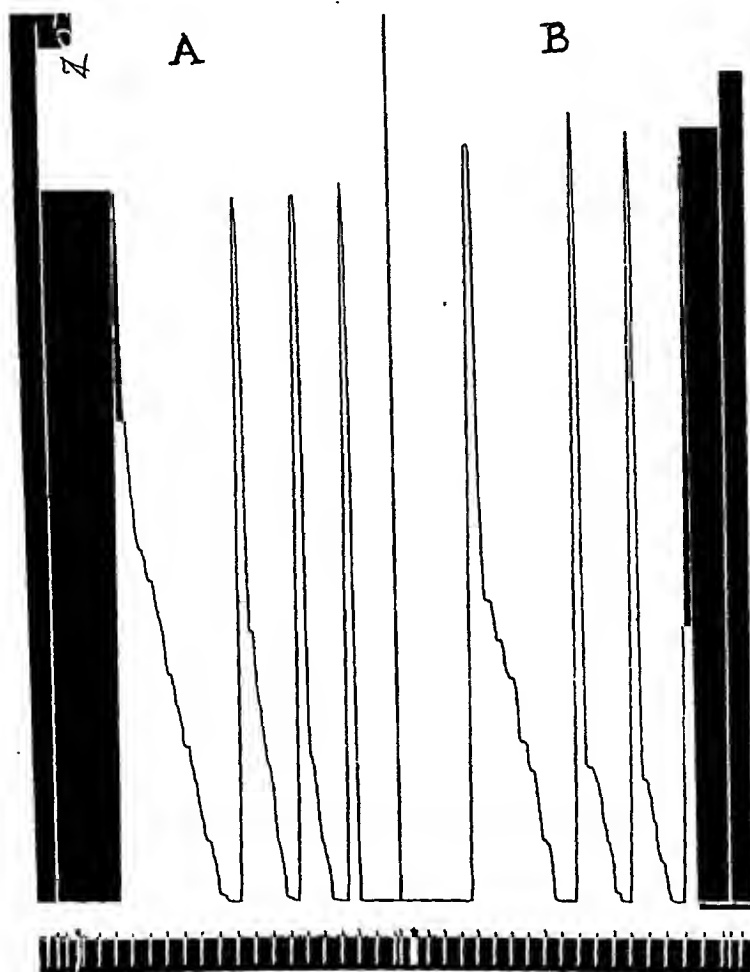


FIG. 1. Movements of the thumb in a patient with dystrophia myotonica; recorded by means of an ergograph and kymograph. Only the muscles producing the upstroke on contraction showed myotonia. The myotonia is evident as the prolongation of relaxation or downstroke. B was taken 10 minutes after A.

Note: the decrease in myotonia in successive contractions and the return of the myotonia after 10 minutes' rest. Time in seconds.

set of muscles results in renewed difficulty, as, for example, beginning to run after having walked. As a corollary of this improvement with repetition of contraction, it follows that the myotonia returns if the muscle is permitted to rest and that myotonia is greatest on the first contraction after a period of rest.

If a muscle which shows myotonia is stimulated to contract by striking it with a percussion hammer, the contraction shows certain peculiarities, most conspicuously a prolongation of the phase of relaxation. The dimple or

furrow formed by the contraction of the stimulated fibers remains visible for many seconds. If small muscles are struck, such as those of the thenar eminence, the muscles often contract as a whole. In such instances, a slow phase of contraction in addition to a slow phase of relaxation is evident. The myotonia decreases with repetition of the percussion but does not usually disappear.

The same phenomenon is seen on producing muscular contraction with an electrical current. Faradic currents of sufficient strength produce myotonic contractions after both nerve and muscle stimulation. With the galvanic current the myotonic contraction is usually evident only after muscle stimulation.

The myotonia seen following voluntary contractions has been called "active or voluntary myotonia," that following mechanical stimulation, "mechanical myotonia," and that following electrical stimulation, "electrical myotonia." The total response of the muscle to electrical and mechanical stimulation has been termed the "myotonic reaction." Any person who shows voluntary myotonia in a few muscles is apt to have mechanical and electrical myotonia of wider distribution.

It is important to note that in each of the above instances the contraction has been voluntarily produced. Myotonia is most commonly confused with persistent contractions of involuntary nature, such as are produced by tetany or irritative nervous system lesions. Involuntary contractions are probably no more common in patients with myotonia than in other persons and when they occur, represent an accidental association.

Voluntary myotonia is affected by certain drugs and a number of conditions, psychic and environmental. Possibly because of an increased strength of contraction, myotonia is much more evident during excitement or fright. It is usually worse under the influence of cold and is improved by warmth. It is not closely dependent upon circulatory conditions.<sup>1</sup> Quinine is a specific for the relief of myotonia, and when given by mouth or intravenously in sufficient dosage, almost completely but only temporarily abolishes myotonia.<sup>2, 3</sup> The same is true of quinidine.<sup>1</sup> Epinephrine given subcutaneously or intravenously temporarily decreases myotonia in patients with dystrophia myotonica<sup>1</sup> (figure 2). Its effect in patients with myotonia congenita requires further investigation. Calcium given intravenously produces a less marked but definite decrease in myotonia.<sup>1</sup> Probably as a result of the mobilization of epinephrine, insulin decreases myotonia when symptoms of hypoglycemia are present.<sup>1</sup> Prostigmin increases myotonia.<sup>3, 4</sup> Potassium chloride by mouth is said to increase myotonia.<sup>3, 4</sup>

In our studies of dystrophia myotonica, much time has been devoted to investigation of the nature of the defect in myotonia. Myotonia is most commonly compared to veratrine contracture. If a strip of frog's muscle is immersed in a veratrine solution, stimulation no longer produces a rapid contraction and relaxation but results in a rapid contraction followed by a slow relaxation very similar to that seen in myotonia. The relaxation be-

comes more rapid if the stimulation is repeated, but returns to its original level after a period of rest. The resemblance to myotonia is again striking. A similar response to strong electrical stimulation of certain highly susceptible muscles of the frog in the absence of veratrine is known as Tiegel's contracture. The same phenomenon, moreover, can be produced in susceptible frog muscles by suitably spaced electrical stimuli delivered to the nerve supplying the muscle. This is the neuromuscular contracture of Bremer.<sup>5</sup>

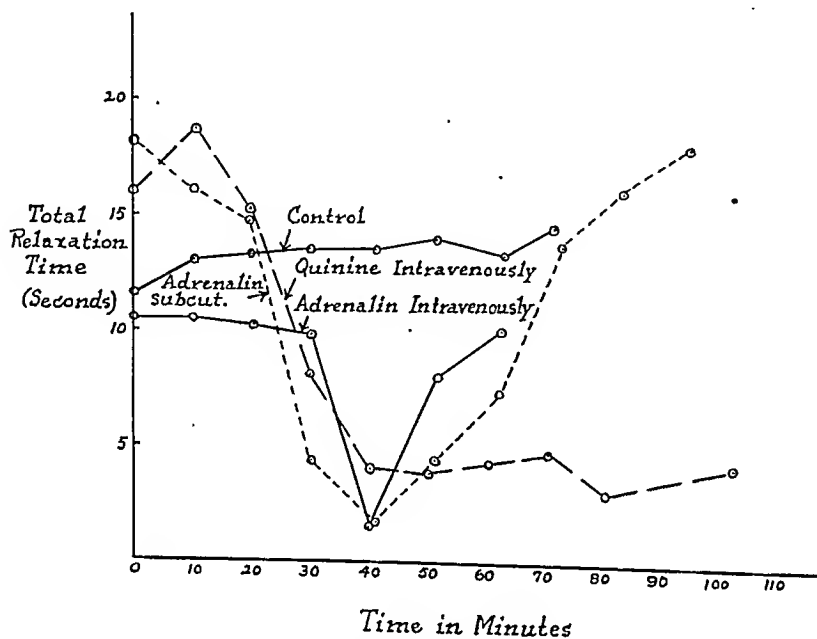


FIG. 2. Effect of adrenalin and quinine on myotonia. Tests of myotonia made at about 10-minute intervals. "Total Relaxation Time" obtained by totalling the times required for relaxation of the first three contractions in each test. Control—at arrow 0.1 c.c. of distilled water was injected. Quinine—at arrow 10 grains of quinine dihydrochloride were injected intravenously. Adrenalin subcutaneously—at arrow 14 mm. of adrenalin hydrochloride (1:1000) were injected. Adrenalin intravenously—at arrow 1½ mm. of adrenalin hydrochloride (1:1000) were injected.

Note: the marked but very fleeting decrease in total relaxation time produced by adrenalin injected intravenously; the marked and somewhat more prolonged effect produced by adrenalin injected subcutaneously; and the marked and prolonged effect of the quinine.

The term "contracture" distinguishes the foregoing type of contraction from a tetanus. A muscle stimulated at such frequent intervals that it remains in a persistent state of contraction is said to be in tetanus. The stimuli cause the fiber as a whole to contract and produce waves of electrical change which travel throughout the length of the muscle fiber. In a contracture the contraction persists for an abnormally long time after the stimulus producing the contraction has ceased acting. The wave-like electrical variations are not present and the shortening is not propagated through the fiber as in the tetanus but may remain localized.<sup>6</sup> Contracture and tetanus are believed by most investigators to involve the same contractile mechanism and the same energy metabolism. Normal muscles are thus seen to possess the property to respond under certain conditions by a contracture. This prop-

erty of responding by contracture varies in degree in different muscles and can be brought out by some drugs.

The relationship of myotonia and contractures is emphasized by the work of Mosso <sup>7</sup> and of Schäffer <sup>8</sup> on the electrical stimulation of the muscles of man. They found that on repeated stimulation of the forearm muscles with strong electrical currents, they could produce a Tiegel's contracture in many normal individuals. It is, therefore, evident that in the human muscle, under certain conditions of stimulation, the capacity to respond by contracture is present. All of the types of contractures mentioned as well as myotonia show the property of fatigability, that is, decrease in duration with repetition of the contraction. The similarity in response to drugs of myotonia and of the contractures is shown in table 1. It may reasonably be concluded that myotonia is closely related to the group of contractures and that the defect in myotonia may be an inherited increase in the tendency of the muscle to respond by contracture.

TABLE I  
Comparison of the Effect of Drugs on Myotonia and Several Contractures

	Decrease with Repetition	Quinine	Adrenalin	Atropine	Eserine — Prostigmin	Calcium
Myotonia	Present	Decrease	Decrease	Decrease?	Increase	Decrease
Tiegel's Contracture in Man	Present		Decrease	Decrease	Increase	
Tiegel's Contracture in Frogs	Present		No Effect	Decrease		
Veratrine Contracture	Present	Decrease	No Effect	Decrease		Decrease
Neuromuscular Contracture	Present	Decrease	No Effect	Decrease	Increase	

#### OCCURRENCE OF MYOTONIA

*Myotonia Congenita.* Myotonia is the well known and striking symptom of Thomsen's disease or myotonia congenita. This hereditary condition is transmitted as a single factor dominant; that is, one half of the children of a person affected with myotonia congenita are likewise affected but none of the children of unaffected members of the family manifest the disease. The myotonia usually begins in the first decade, occasionally in the second, and persists throughout life although in some families it has been reported to become less severe as the individuals become older. Most of the skeletal muscles are involved and the affected muscles show a hypertrophy which gives these persons a marked athletic appearance out of proportion to their actual strength. On initiating any new movement they are brought up short by the myotonic contractions and soon learn to avoid sudden move-

ments. By "warming up" before attempting any marked exertion, many embarrassing situations are avoided. Myotonia congenita is not a fatal malady but until the discovery of the beneficial effect of quinine, little could be done to ameliorate the disability. Quinine in doses of 15 to 30 grains per day by mouth affords great relief.

*Dystrophia Myotonica.* Although less generally known to the medical profession than myotonia congenita, this condition is much more common. Many of these cases are diagnosed myotonia congenita and many more, progressive muscular atrophy. The disease appears to occur rather explosively in many members of one generation, the members of the previous generation being apparently normal. Examination of family trees shows, however, that the parents of dystrophic patients do show evidences of the disease and it is our belief that the disease is transmitted as a dominant characteristic modified, however, by "progressive inheritance." Parents of patients with the disease have a mild form of the disease but affected children of patients have the disease in a more severe form and at an earlier age.<sup>9</sup>

In this disease the myotonia is limited in distribution and constitutes a relatively unimportant part of the symptom complex. It occurs mainly in the hand grasps, occasionally in the muscles of mastication and in the legs. Rarely it may be widespread. The most important feature of the disease is the progressive muscular atrophy. In early stages this atrophy shows a characteristic pattern of involvement which includes the muscles of the face, the sternocleidomastoids, the muscles of the forearm, the quadriceps, and the dorsiflexors of the feet. In more advanced stages most of the muscles of the body are involved. In addition to the myotonia and atrophy, many other dystrophic changes occur. A rather characteristic cataract is almost always found if slit lamp examination is done. Testicular atrophy, baldness, and low basal metabolic rate frequently form the remainder of the picture. The condition progresses slowly but inexorably and, unlike myotonia congenita, many of these patients die of the disease. Quinine improves the myotonia; cataract operation improves vision; but nothing has yet been found to stay the progress of the disabling atrophy.<sup>10</sup>

*Myotonia Congenita Intermittens* and *Paramyotonia Congenita* (Sölder-Schott). Rare families have been described whose affected members are normal in warm weather but show muscular difficulties under the influence of cold. In some families myotonia alone occurs, in others the myotonia is associated with a marked muscle weakness, and in still others the muscle weakness occurs alone. The condition is inherited and appears to be a single factor dominant. The muscles involved are mainly those of the upper extremities and of the face; the legs are involved only in severe cold. When the cold results in myotonia without weakness, it is preferable to label the condition *myotonia congenita intermittens*.<sup>11</sup> When a marked muscular weakness occurs in addition to the myotonia the condition has usually been called *paramyotonia congenita* because of confusion with the disease de-

scribed by Eulenburg.<sup>12</sup> In paramyotonia congenita as described by Eulenburg there are no myotonic contractions in warmth or cold and the essential feature is the occurrence in the cold of spontaneous cramps followed by a weakness simulating paralysis. One such family has been described in America by Rich.<sup>13</sup> Rather than use a new name for the disease in which myotonia occurs in addition to weakness, we have retained the name of paramyotonia congenita but qualified it by adding the names of two men who have described such families. We may thus speak of the paramyotonia congenita of Sölder<sup>14</sup> and Schott<sup>15</sup> and the paramyotonia congenita of Eulenburg.

*Myotonia Acquisita.* Many cases have been reported in the literature in which myotonia has occurred sporadically following an injury or illness in individuals having no hereditary background. In 1934 Krabbe<sup>16</sup> collected 34 such cases from the literature and added one of his own. Examination of such cases shows that they fall into three groups:

(1) Patients in whom the condition described is definitely not myotonia, but various types of intention spasms and involuntary contractions which do not fulfill the criteria for myotonia.

(2) Patients in whom the hereditary features have been overlooked because of incomplete investigation. The nature of the inheritance in dystrophia myotonica is such that it is not always evident. Any patient showing any evidence of the atrophy characteristic of dystrophia myotonica or the cataract must be excluded from the group of acquired myotonias. When it is recalled that the myotonia may be the earliest sign of dystrophia myotonica it is evident how cautious one must be in making a diagnosis of myotonia acquisita. In families with myotonia congenita the patient's statement that none of the other members of the family are affected is not sufficient to rule out heredity. The members of families affected with myotonia show the same variation in the degree of involvement which is characteristic of members of families affected with other hereditary conditions. It is well known, for example, that in some members of polydactylous families the defect can be recognized only by roentgen-ray. Likewise, myotonia may be so mild in the affected parent as to be overlooked.

(3) A very small group of patients in whom it seems possible that a true myotonia has temporarily manifested itself after some injury and in whom the hereditary factor appears ruled out.

It seems safe to conclude that, if myotonia acquisita does occur, it is quite rare, unless one considers the syndrome described below as falling under that heading.

*Syndrome of Hypothyroidism, Muscle Hypertrophy, and Myotonia.* Examination of the literature shows approximately a dozen cases<sup>17-25</sup> in which hypothyroidism, muscle hypertrophy, and myotonia have been combined to form a remarkably uniform picture. They have been reported as

cases of myxedema with unusual muscle phenomena, as cases of myotonia congenita, and as cases of muscle hypertrophy of unknown origin.

The hypothyroidism is usually very evident, with the characteristic facies, the skin changes, the mental changes, and even the cardiovascular changes. The hypothyroidism may be congenital, follow thyroidectomy, or occur spontaneously in adults of either sex and of any age.

The muscle hypertrophy is most striking in infants but occurs also in adults. Although usually quite generalized it is often more marked in the extremities. The muscles are firm and the muscle strength does not correspond to the bulk.

Not all forms of myotonia are always found. The mechanical myotonia is most marked and most frequently reported. Voluntary myotonia is not marked in any case and often reported as absent. Electrical myotonia is usually present but differs in minor details from the electrical myotonia seen in myotonia congenita.

In many patients evidences of hypertonicity of the muscles are present. In the infant severe spasms sometimes occur and resistance to passive motion is present. In adults hypertonicity is evident as painful contractions which come on usually with sudden or forcible movements.

With thyroid therapy marked improvement occurs in the muscle symptoms as well as in the symptoms of hypothyroidism. From the effect of thyroid therapy it must be concluded that the entire syndrome is the result of thyroid deficiency. We have been investigating patients with myxedema and have found repeatedly a clear-cut although short mechanical myotonia. It is our belief that probably all patients with marked myxedema show slight or moderate evidence of the above changes but that the entire syndrome occurs only in persons with some inherited defect. This defect may not be the same as that which results in true myotonia.

#### SUMMARY

1. The muscles of some persons remain contracted for an abnormally long time after voluntary effort to contract them has ceased. This muscular abnormality is called myotonia and is manifest as a delay in muscular relaxation.

2. In a series of contractions myotonia diminishes each time the contraction is repeated. Correspondingly it is worse after a period of rest. Myotonia is not painful; it increases with increase in force of contraction.

3. Myotonia associated with voluntary contractions is called "active or voluntary myotonia." Myotonia associated with contractions produced by mechanical or electrical stimuli is known respectively as "mechanical myotonia" and "electrical myotonia."

4. Voluntary myotonia is decreased by quinine, by adrenalin, by calcium given intravenously, and by insulin when symptoms of hypoglycemia are present.



5. A comparison of the characteristics of myotonia with those of several contractures suggests that myotonia may be a contracture.
6. Myotonia occurs classically in myotonia congenita.
7. Myotonia occurs most commonly in dystrophia myotonica.
8. Rarely myotonia occurs only under the influence of cold.
9. Myotonia occurs infrequently in persons without a hereditary background.
10. In the severely hypothyroid state some persons show, in addition to the usual signs of hypothyroidism, muscular hypertrophy and myotonia.

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# CARDIOVASCULAR EFFECTS OF LARGE DOSES OF METRAZOL AS EMPLOYED IN THE TREATMENT OF SCHIZOPHRENIA \*

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SINCE von Meduna<sup>1</sup> first reported his success in the treatment of schizophrenia by the induction of convulsions with metrazol, his method has enjoyed considerable popularity, and has been employed in many hundreds of cases.

His method consists essentially in the repeated (three times weekly) induction of severe epileptiform convulsions of a specific type by the rapid intravenous injection of large doses of metrazol (pentamethylenetetrazol, formerly known as cardiazol), in a 10 per cent aqueous solution. The initial dose usually employed is 3 to 5 c.c. and it is usually increased progressively so that convulsions are regularly obtained—until a course of treatment producing 20 to 30 convulsions has been administered. Such a schedule at times necessitates pushing up the individual injection dose to amounts as high as 25 c.c., and it is quite usual for doses of 12 to 15 c.c. to be reached in the average case.

In view of the original introduction and use of this drug as a cardio-respiratory stimulant (as the name cardiazol implied), and then generally only in doses of 1 to 2 c.c. administered subcutaneously or intramuscularly, it is not surprising that we frequently hear expressed concern about the possible danger to the heart of employing such massive doses intravenously. The purpose of this paper is to supply a definite answer to this question.

A priori one might assume that there are no significant dangers to the cardiovascular system inherent in the metrazol treatment because in the numerous cases treated no serious cardiovascular complications have been reported.

The solitary instance of cardiac death reported in the literature (L. von Angyal and K. Gyárfás<sup>2</sup> obviously should not be attributed to the therapy but to improper case selection: A female patient, aged 31, was given her second injection, 0.7 gm. of metrazol and did not have a seizure; however, one-half hour later she suddenly collapsed and died. Autopsy showed an *old* aortic insufficiency and myocardial degeneration.

A survey of the published literature affords the following sketchy information: Friedman<sup>3</sup> states: "The entire sympathetic nervous system is

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stimulated: for example, rapid changes of skin color, goose flesh, profuse sweating, changes in cardiac rate and blood pressure, stimulation of the entire alimentary tract, bladder incontinence, ejaculation." He does not specify what the cardiovascular changes are.

Finkelman et al.<sup>4</sup> state: "The blood pressure rises from 20 to 60 mm. of mercury during the seizure and drops to its normal level in from 10 to 30 minutes."

L. Kruger<sup>5</sup> remarks: "Pulse rate and quality were but slightly affected. Cardiac function showed no more changes than occur with any convulsion."

L. v. Meduna<sup>6</sup> cites Lax as follows: "An electrocardiogram was taken in 11 patients who underwent cardiazol therapy. Sometimes the electrocardiogram was taken before, and sometimes after the convulsion. In 5 cases an electrocardiogram was taken during the convulsion and then 10-15 minutes afterwards. We could find no noteworthy changes from the ones taken before the convulsions and serving as controls. As a further check, 8 patients had electrocardiograms taken 2-4-6 or 1-3-5 hours after the convulsion. In 4 cases there was a minimal depression of the T-wave as compared with the records made before the convulsion. There was no change detected in the P-wave or ventricular complex in height, or time interval, nor any alteration in the rhythm or signs of ectopic origin. In conclusion we may say: Up to the present our investigations seem to show no changes in the electrocardiogram indicative of myocardial damage after cardiazol convulsions."

In a paper devoted primarily to the effects of crystalline insulin on the blood pressure and electrocardiogram, Heinrich and Sussner<sup>13</sup> state that when metrazol was administered the decrease in blood pressure, which lasted only seconds, was followed by an increase that persisted for minutes. Electrocardiographic tests frequently revealed that the T-wave, which had become lower under the influence of crystalline insulin, showed a tendency to rise again. The effect of metrazol on the frequency varied in that acceleration or retardation occurred.

Hadorn<sup>14</sup> also has made some electrocardiographic studies in metrazol shock. He found that metrazol shock therapy does not cause the same electrocardiographic changes as does the insulin shock; nevertheless it does cause changes, particularly in the auricular activity. The electrocardiograms that are made after metrazol shock reveal chiefly sinus tachycardias and a tendency to extrasystoles and auricular fibrillation. Changes in the S-T section and in the T-wave, which characterize insulin shock, are absent.

A review of the literature on work performed with metrazol on experimental animals also discloses quite meager and, in some respects, conflicting data as regard its cardiovascular effects: Thus, E. A. Müller<sup>7</sup> reports: "Experiments on intact animals (dogs) showed that with strong depression of the heart and circulatory activity by deep narcosis, cardiazol produced a definite long lasting elevation of blood pressure and minute volume to the normal level. The increased blood pressure is not merely the result of the

increased minute volume but is also due to increased peripheral resistance. The heart adapts immediately or in a short time to the increased circulatory work-load. The cause of this adjustment is *not* a direct effect of the cardiazol on the heart, as is shown by heart-lung preparation experiments, but rather of an improved coronary circulation, which is partly a result of the increased blood pressure, and partly a consequence of the direct widening effect of cardiazol on the coronary vessels." This worker conducted his experiments on only three dogs, and claims he secured an increased coronary flow "ranging from 1 per cent to 22 per cent," using doses of metrazol ranging from 10 to 100 mg. intravenously. Thus, his maximum dose corresponds to a dose of 9 c.c. (0.9 gram) applied to a 60 kilogram human. He made no electrocardiographic studies.

On the other hand, Stoland and Ginsberg<sup>8</sup> state: "Data on the intact animal warrant the conclusion that metrazol has no important effect on coronary flow, blood pressure, or heart rate." They also had worked on dogs and their maximum dose corresponded to a dose of 6 c.c. (0.6 gram) for a 60 kilogram human.

As regards the use of metrazol in the routine combating of postanesthetic depression, K. Schlaepfer<sup>9</sup> states: "Metrazol does not appear to have a local effect on the blood vessels, but a central stimulation brings about an increase in the tone of the vascular wall, followed by a rise of a *lowered* blood pressure. Apparently, the drug has little or no effect on the normal blood pressure of a normal individual."

Since the sources quoted above present so few detailed physiological or electrocardiographic studies of the effect of the metrazol treatment on the cardiovascular system, we feel that more information should be made available.

Our case material consisted of 14 psychotic male patients ranging in age from 26 to 46 years. One patient's age fell in the third decade, two fell in the fourth, and the remainder in the fifth decade, so that their average age was well over 40. Ten of the patients had had one or more previous complete courses of Sakel's insulin treatment, but in every case at least two months had elapsed since the insulin treatment was completed before metrazol was begun. Only two cases (numbers 6 and 7) had had no previous pharmacological shock treatment. We shall group our observations under the two headings of clinical and electrocardiographic findings:

### I. CLINICAL FINDINGS

The dramatic picture of the patient's appearance during the metrazol convulsion has often been adequately described in the literature. Moreover, various workers in this field have made color movies of the seizures and thus graphically recorded the color changes. From all such studies it is clearly apparent that there occurs during the metrazol seizure a profound activation of various vasomotor centers, which is reflected by generalized or regional

blanching or suffusion of different areas of the body surface. It must be borne in mind, however, that the color changes observed are the result not only of the vasomotor activity, but also of the cyanosis which usually develops during the tonic phase of the seizure (and which may persist for some time thereafter because of mechanical obstructions in the air passages), and that they further are modified by the ischemic and congestive changes produced in the skin areas overlying the violently contracting muscles. The variable pictures seen in different patients, and the evident tendency for similar series of vasomotor changes to repeat themselves in the same patients, may be accepted as an indication that the precise nature of the vasomotor reaction in any individual is directly dependent on the particular pattern of vasomotor organization of that individual. It has been our experience that in those instances where the injection of the drug was followed either by no seizures at all or by only an abortive (*petit mal*) type of reaction, the vasomotor changes were less marked or even absent.

Palpation of the pulse usually shows a slight to moderate acceleration (10 to 30 beats per minute) immediately after the seizure, and quite frequently the appearance of some irregularity (occasional extrasystoles) which invariably subsides entirely in a minute or so. Only rarely does a more marked tachycardia (140 to 160 per minute) appear for a minute or so after the fit, but this, too, soon subsides (see items 9 and 10 in the electrocardiogram table). The volume of the pulse is usually well maintained, particularly after the irregularity has disappeared.

Auscultation is obviously impractical during the stormy convulsive episode, but after the breathing has quieted down sufficiently during the post-convulsive phase, the heart sounds are invariably found to be of good quality and regular in rhythm. Careful auscultation for murmurs is also impractical during the postconvulsive comatose, semicomatose, and confused states, so that we made most of our observations for murmurs in the afternoon three to four hours after the metrazol injection. At that time we quite frequently found evidence of the development of the aortic dilatation phenomenon analogous to that which we described in an earlier paper concerned with the cardiovascular effects of insulin treatment.<sup>10</sup> That is, in every treated patient who was properly coöperative we could detect murmurs varying from the faintest systolic blow to a quite marked to and fro blowing murmur at the aortic area and left border of the sternum. The murmurs were very faint and practically insignificant (listed as one plus) in half of our patients. When they were more definite (listed as two to three plus) in the other six patients, they were not as marked as the murmurs these same patients had shown while under the insulin treatment, and similarly these same patients did not show as great an increase in pulse pressure while under metrazol treatment as they had shown while under insulin treatment. Since the two patients who had not been previously treated with insulin fell in the group which showed only minimal (one plus) murmurs, we cannot conclude that metrazol *alone* is a profound sympathetic (adrenalin-mimetic) stimulant

of the cardiovascular apparatus. It may be that in those cases which were more sensitive it had merely reactivated a latent sympathetic susceptibility which had originally been markedly augmented by the previous course of insulin treatment.

In order to determine the effects of metrazol injections on the blood pressure, studies were made in connection with some (72) metrazol injections administered to 12 different patients. Thirty-three of these observations were made on patients who were receiving metrazol alone, the remainder being made on patients who received metrazol in conjunction with insulin during the third hypoglycemic hour. All blood pressure readings were made by the same observer (N. M.) by the auscultatory method, using a mercury sphygmomanometer. Readings were made in each instance immediately before the metrazol injection, and then again as soon as possible after the convulsive reaction had ended. This second reading was usually feasible within 5 to 10 seconds after the last convulsive twitch. In many cases subsequent readings were taken at minute intervals. In those instances where a typical "grand mal" or "petit mal" type of convulsion did not result from the metrazol injection, the second reading was taken within one minute after completion of the injection. The position of the sphygmomanometer cuff was not changed between the two readings, the intravenous metrazol injection being given into the other arm.

We have listed the results of the blood pressure readings in tabular form according to the type of metrazol reaction which followed the injection. In table A we have listed the cases in which the injection was followed *only by slight stimulation*, as manifested by a slight twitching of the eyes, startled expression, and subjective "dazed" feeling. In table B we have listed the cases in which the injection was followed by a "*petit mal*" type of reaction as manifested by more or less prolonged definite clonic movements often associated with marked mental excitement and not followed by any appreciable state of coma. In table C we have listed the cases in which the injection was followed by the typical metrazol "grand mal" type of reaction consisting of first clonic, tonic, and second clonic phases, terminating in a state of coma.

It may be observed from these tables that the blood pressure changes in connection with metrazol treatment coincide *primarily* with the state of *emotional excitement* and *mental awareness* of the patient at the time the reading is taken. (This relationship is clearly indicated by study of the notes made in the "Remarks" column of the table.) The blood pressure changes do not appear to have any special relationship to the amount of drug injected. The type of physical reaction induced by the injection seems to influence the blood pressure only in so far as it determines to a large extent the mental and emotional state of the patient at the time the readings are taken. Thus, the figures in table A (in which are grouped the blood pressure readings before and after injections in which "stimulation only" was obtained) indicate a definite trend towards a slight elevation of systolic, diastolic, and

pulse pressure in these cases. Thus, five instances in which metrazol alone was used and "stimulation only" resulted gave an average systolic blood pressure rise of 9 mm. of mercury, with an average diastolic rise of 2.8 mm.

The figures in table B (in which are grouped the blood pressure readings before and after injections in which a "petit mal" type of reaction was obtained) indicate a definite trend towards a *moderate* elevation of systolic and diastolic pressures.

The figures in table C (in which are grouped the blood pressure readings before and after injections in which a "grand mal" type of reaction was obtained, and in which consequently the postconvulsive reading was taken in a state of more or less complete coma) indicate a definite trend towards a moderate drop in the systolic and diastolic pressures as an immediate consequence of the fit.

Blood pressures taken during the preconvulsive interval (that is, before the intravenously injected drug has had an opportunity to exert any visible effect on the nervous system) invariably show no significant change when compared with those taken before the metrazol injection (see items number 2 and 3 in table B<sub>1</sub>, and items number 8, 15, 16, 20, 21, and 23 in table C<sub>1</sub>).

Blood pressures taken in succession during the postcomatose "awakening" stage show a progressive increase which pretty well corresponds to the state of mental awareness and excitement clinically evident. (See items number 9, 7, 8, 21, 13, 16, 22 of table C<sub>1</sub>, and numbers 7, 16, 8, 20, 4 of table C<sub>2</sub>.) Blood pressures taken after the patient is again fully conscious and recovered from the fit, as well as blood pressures taken in the afternoon several hours after the fit, show no significant variation from their usual normal level.

In those instances in which the metrazol was given when the patient was in a state of hypoglycemic shock, the blood pressure changes generally were in the same direction but rather more marked in degree than in those cases in which metrazol was given alone (compare tables A<sub>2</sub> with A<sub>1</sub>, B<sub>2</sub> with B<sub>1</sub>, C<sub>2</sub> with C<sub>1</sub>). This would seem to indicate that the administration of the insulin had caused an increase in the cardiovascular lability of these patients. This finding is in accord with our concepts of the cardiovascular effects of insulin treatment, as previously reported.<sup>10</sup>

The preponderant influence of the emotional status of the patient on the extent of the blood pressure changes following the injection of metrazol is more clearly indicated when one considers only those cases in which an evident state of fear or excitement was noted at the time of the injection. Such a state was noted nine times when metrazol alone was used (table C<sub>1</sub>) and four times when metrazol was given after insulin (table C<sub>2</sub>). The readings in these instances are distinguished from the others by the placing of a "plus" sign in the last column of the blood pressure tables. The figures from table C<sub>1</sub> show that in the instances in which there was obvious fear and excitement the average systolic blood pressure change was minus 21.9 mm. as compared with a general average systolic change of minus 9.3 mm.



TABLE A  
Effects of Metrazol on Blood Pressure

Type of Reaction	Item No.	Initials, Case No. Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Sys-tolic B.P. Change	Dia-stolic B.P. Change	Pulse Pres-sure Change
A: "Stimula-tion only."	1	M. B. No. 6 6-6-38	5 c.c. Metrazol	162/92	170/98	Patient very fearful, apprehensive, and ex-cited both before and after the injection	+ 8	+6	+ 2
	2	M. B. No. 6 6-11-38	6.2 c.c. Metrazol	132/74	140/78	Patient moderately apprehensive, but com-pliant to treatment	+ 8	+4	+ 4
	3	E. D. No. 2 6-15-38	5.2 c.c. Metrazol	134/82	140/80	126/78 (immediately after) $\rightarrow$ $\frac{140}{80}$ (1 min.) $\rightarrow$ $\frac{142}{80}$ (2 min.)	+ 6	-2	+ 8
A <sub>1</sub> : Metrazol alone	4	E. D. No. 2 6-15-38	5.6 c.c. Metrazol	140/76	142/82	No reaction, 140/78 immediately after $\rightarrow$ $\frac{142}{82}$ (1 min.)	+ 2	+6	- 4
	5	H. T. No. 3 6-17-38	5.2 c.c. Metrazol	135/72	156/72	Slight stimulation only (EKG taken)	+21	0	+21
A <sub>2</sub> : Insulin and Metra-zol	1	B. V. D. No. 4 5-20-38	3.8 c.c. Metrazol 120 u. Ins.	124/46	144/52	Patient drowsy prior to injection—not ap-prehensive	+20	+6	+14
	2	B. V. D. No. 4 5-25-38	5 c.c. Metrazol 120 u. Ins.	154/66	165/66	Slight stimulation only	+14	0	+14
	3	C. W. No. 13 5-25-38	3 c.c. Metrazol 30 u. Ins.	120/74	142/90	Patient in light insulin coma at time of M. injection	+22	+16	+ 6
	4	G. V. No. 11 6- 6-38	4.4 c.c. Metrazol 80 u. Ins.	122/70	136/76		+14	+6	+ 8
	5	H. K. No. 12 6- 9-38	3 c.c. Metrazol 15 u. Ins.	106/76	110/80	Single slight quiver	+ 4	+4	0

{ Range of Systolic B.P. Changes = +2 to +21; Average Syst. B.P. Change = +9  
 A<sub>1</sub> { Range of Diastolic B.P. Changes = -2 to +6; Average Diast. B.P. Change = +2.8  
 { Range of Pulse Pressure Changes = -4 to +21; Average Pulse Pressure Change = +6.2.  
 A<sub>2</sub> { Range of Systolic B.P. Changes = +4 to +22; Average Syst. B.P. Change = +14.8  
 { Range of Diastolic B.P. Changes = 0 to +16; Average Diast. B.P. Change = +6.4  
 { Range of Pulse Pressure Changes = 0 to +14; Average Pulse Pressure Change = +8.4.

TABLE B  
Effects of Metrazol on Blood Pressure

Type of Reaction	Item No.	Initials Case No. Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Systolic B.P. Change	Diastolic B.P. Change	Pulse Pressure Change
B: "Petit Mal" B <sub>1</sub> : Metrazol alone	1	M. C. No. 7 5-25-38	12.8 c.c. Met.	150/80	162/82		+12	+2	+10
	2	M. C. No. 7 6-17-38	13 c.c. Met.	154/80	150/90	1st phase only—duration 45 seconds B.P. 152/88 during preconvulsive interval	-4	+10	-14
	3	M. C. No. 7 6-21-38	13 c.c. Met.	160/90	192/100	1st phase only; 2 minutes later, quiet-162/88. B.P. 156 systoles during preconvulsive interval	+32	+10	+22
B <sub>2</sub> : Insulin and Metrazol	1	F. S. No. 8 5-20-38	8.4 c.c. Met. 120 u. Ins.	144/74	172/78		+28	+4	+24
	2	F. S. No. 8 5-21-38	8.6 c.c. Met. 120 u. Ins.	130/72	148/82	Marked excitement after injection	+18	+10	+8
	3	F. S. No. 8 6-11-38	9.4 c.c. Met. 120 u. Ins.	128/82	144/86	Prolonged 1st phase with marked excitement	+16	+4	+12
	4	C. P. No. 10 5-28-38	3.6 c.c. Met. 100 u. Ins.	122/70	120/72		-2	+2	-4
	5	C. P. No. 10 6-8-38	5.8 c.c. Met. 120 u. Ins.	122/0	126/0	10 minutes later = 124/76	+4	0	+4
	6	C. W. No. 13 6-8-38	4 c.c. Met. 30 u. Ins.	130/92	148/94	Struggling after injection	+18	+2	+16

{ Range of Systolic B.P. Changes = -4 to +32; Average Systolic B.P. Change = +13.3  
 B<sub>1</sub> { Range of Diastolic B.P. Changes = +2 to +10; Average Diastolic B.P. Change = +7.3  
 { Range of Pulse Pressure Changes = -14 to +22; Average Pulse Pressure Change = +6  
 B<sub>2</sub> { Range of Systolic B.P. Changes = -2 to +28; Average Systolic B.P. Change = +16.4  
 { Range of Diastolic B.P. Changes = 0 to +10; Average Diastolic B.P. Change = +4.4  
 { Range of Pulse Pressure Changes = -4 to +24; Average Pulse Pressure Change = +12.

TABLE C<sub>I</sub>  
Effects of Metrazol on Blood Pressure

Type of Reaction	Item No.	Initials, Case No., Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Systolic B.P. Change	Diastolic B.P. Change	Pulse Pressure Change	Cases Showing Obvious Excitement before Injection
C: "Grand Mal" C <sub>1</sub> : Using Metrazol only	1	M. C. No. 7 5-20-38	12.4 c.c.	148/80	190/90		+42	+10	+32	
	2	M. C. No. 7 5-28-38	13 c.c.	140/72	146/82		+6	+10	-4	
	3	M. C. No. 7 6-1-38	13 c.c.	165/86	142/68	Fearful and excited before injection	-23	-18	-5	+
	4	M. C. No. 7 6-6-38	13 c.c.	170/92	142/84	Fearful and excited before injection	-28	-8	-20	+
	5	M. C. No. 7 6-8-38	13 c.c.	164/76	128/68	Excited and struggling before injection	-36	-8	-28	+
	6	M. C. No. 7 6-11-38	13 c.c.	164/92	132/86	Very fearful before injection	-32	-6	-26	+
	7	M. C. No. 7 6-13-38	13 c.c.	150/90	138/78	B.P. 152/90 one minute later (awaking from coma)	-12	-12	0	
	8	M. C. No. 7 6-15-38	13 c.c.	154/86	144/80	B.P. 148 systolic in preconvulsive interval; B.P. 158/96 one minute after fit (awaking from coma)	-10	-6	-4	
	9	M. B. No. 6 6-8-38	6 c.c.	128/78	130/82	B.P. 152/90 one minute later (awaking from coma)	+2	+4	-2	
	10	M. B. No. 6 6-13-38	6.6 c.c.	136/76	152/96	B.P. 170/96 during late clonic phase	+16	+20	-4	
	11	M. B. No. 6 6-15-38	6.8 c.c.	152/92	136/80	Fearful and pleading before injection	-16	-12	-4	+
	12	M. B. No. 6 6-17-38	7 c.c.	138/78	118/62	Fearful and pleading before injection	-20	-16	-4	+
	13	M. B. No. 6 6-21-38	7.2 c.c.	154/90	148/62	Very fearful before injection. B.P. 172/92 two minutes later (awaking from coma)	-6	-28	+22	+
	14	M. B. No. 6 6-24-38	7.4 c.c.	146/78	138/68		-8	-10	+2	
	15	E. D. No. 2 6-13-38	5 c.c.	126/72	150/84	Systolic B.P. 130 just before convulsion began; pre-convulsive interval prolonged to 50 seconds	+24	+12	+12	

TABLE C1—Continued

Type of Reaction	Item No.	Initials Case No., Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Systolic B.P. Change	Diastolic B.P. Change	Pulse Pressure Change	Cases Showing Obvious Excitement before Injection
	16	E. D. No. 2 6-21-38	6 c.c.	140/74	140/78	Preconvulsive interval prolonged to 40 seconds; B.P. during preconvulsive interval = 136/76. B.P. two minutes after fit = 162/98 (awaking from coma)	0	+4	-4	
	17	R. M. No. 14 6-13-38	4 c.c.	148/82	150/80	Pulse quite irregular and rapid (rate 160) for first couple of minutes after fit	+2	-2	+4	
	18	R. M. No. 14 6-15-38	4.2 c.c.	162/72	140/72	Excited before injection	-22	0	-22	+
	19	R. M. No. 14 6-17-38	4.4 c.c.	152/86	148/78	EKG taken while awaking from coma (two minutes after fit)	-4	-8	+4	
	20	R. M. No. 14 6-24-38	4.8 c.c.	162/84	148/80	Fearful before injection. Systolic B.P. during preconvulsive interval = 172	-14	-4	-10	+
	21	H. T. No. 3 6-15-38	5 c.c.	136/70	90/0	Preconvulsive interval prolonged to 44 seconds; B.P. during preconvulsive interval = 140/78; B.P. 1 min. after fit = 110/0 B.P. 2 min. after fit = 122/0 B.P. 4 hrs. later = 134/82 EKG taken 20 sec. after end of fit. B.P. 122/70 2 min. later (while Lead IV of EKG was being recorded)	-46	-70	+24	
	22	H. T. No. 3 6-21-38	6 c.c.	138/74	118/44	B.P. during preconvulsive interval = 142/90	-20	-30	+10	
	23	H. T. No. 3 6-24-38	6.2 c.c.	130/74	122/72		-8	-2	-6	

Range of Systolic B.P. Changes = -46 to 42; Average Syst. B.P. Change = -9.3; Aver. Syst. Change  $\bar{c}$  "E" = -21.9.  
 Range of Diastolic B.P. Changes = -70 to +20; Average Dias. B.P. Change = -7.8; Aver. Dias. Change  $\bar{c}$  "E" = -11.1.  
 Range of Pulse Pressure Changes = -28 to +32; Average P.P. Change = -1.4; Aver. P.P. Change  $\bar{c}$  "E" = -10.8.  
 Number instances with obvious excitement = 9(+) (with excitement changes were always downward).

TABLE CII  
Effects of Metrazol on Blood Pressure

Type of Reaction	Item No.	Initials, Case No. Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Systolic B.P. Change	Diastolic B.P. Change	Pulse Pressure Change	Cases Showing Obvious Excitement before Injection
C: "Grand Mal" C <sub>2</sub> ; Using Insulin and Metrazol	1	G. V. No. 11 5-20-38	80 u. Ins. 4 c.c. Met.	124/64	132/70		+ 8	+ 6	+ 2	
	2	G. V. No. 11 5-26-38	80 u. Ins. 4.4 c.c. Met.	112/80	110/70		- 2	- 10	+ 8	
	3	G. V. No. 11 6-1-38	80 u. Ins. 4.4 c.c. Met.	124/88	112/76		- 12	- 12	0	
	4	G. V. No. 11 6-9-38	80 u. Ins. 4.8 c.c. Met.	128/68	90/30	B.P. 110/56 one-half minute later—130/72 one minute later	- 38	- 38	0	
	5	G. V. No. 11 6-9-38	120 u. Ins. 8.8 c.c. Met.	182/114	132/78	Fearful before injection	- 50	- 36	- 14	+
	6	G. V. No. 11 6-9-38	80 u. Ins. 8.8 c.c. Met.	118/74	98/66		- 20	- 8	- 12	
	7	G. U. No. 9 5-25-38	4.8 c.c. Met. 120 u. Ins. 8.8 c.c. Met.	200/108	162/92	Fearful before injection; B.P. 202/90, 5 min. later (awaking from coma)	- 38	- 16	- 22	+
	8	G. U. No. 9 5-25-38	120 u. Ins. 8.8 c.c. Met.	196/108	148/86	Fearful before injection; B.P. 160/90, 172/92, two and four minutes later (awaking from coma)	- 48	- 22	- 26	+
	9	G. U. No. 9 5-28-38	120 u. Ins. 8.8 c.c. Met.	168/94	174/86		+ 6	- 8	+ 14	
	10	G. U. No. 9 6-1-38	120 u. Ins. 8.8 c.c. Met.	170/108	156/76		- 14	- 32	+ 18	
	11	G. U. No. 9 6-8-38	120 u. Ins. 8.8 c.c. Met.	190/108	154/74		- 36	- 34	- 4	+
	12	C. P. No. 10 5-20-38	100 u. Ins. 3.6 c.c. Met.	122/78	138/78	Fearful before injection	+ 16	0	+ 16	
	13	C. P. No. 10 6-1-38	100 u. Ins. 4 c.c. Met.	112/72	118/76		+ 6	+ 4	+ 2	
	14	C. P. No. 10 6-6-38	100 u. Ins. 4 c.c. Met.	122/68	126/68		+ 4	0	+ 4	
	15	C. P. No. 10 6-9-38	100 u. Ins. 4.2 c.c. Met.	124/0	114/42		- 10	+ 42	- 52	
	16	B. V. D. No. 4 5-21-38	120 u. Ins. 4.2 c.c. Met.	138/52	110/40	B.P. 160/54 two min. later (post convulsive confused excitement developing); B.P. 174/44 four minutes later; B.P. 136/60 thirty minutes later (awake, calm, reading newspaper)	- 28	- 12	- 16	

TABLE CII—Continued

Type of Reaction	Item No.	Initials, Case No., Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Systolic B.P. Change	Diastolic B.P. Change	Pulse Pressure Change	Cases Showing Obvious Excitement before Injection
	17	B. V. D. No. 4 5-26-38	120 u. Ins. 5.4 c.c. Met.	128/66	150/48		+22	-18	+40	
	18	B. V. D. No. 4 5-28-38	120 u. Ins. 5.4 c.c. Met.	126/66	120/52		-6	-14	+8	
	19	B. V. D. No. 4 6-1-38	120 u. Ins. 5.4 c.c. Met.	138/60	130/50		+8	+10	-2	
	20	B. V. D. No. 4 6-6-38	120 u. Ins. 5.8 c.c. Met.	148/46	150/12	B.P. 172/40 one minute later (beginning to awake from deep coma)	+2	-34	+36	
	21	B. V. D. No. 4 6-8-38	120 u. Ins. 3.2 c.c. Met.	136/72	116/0		-20	-72	+52	
	22	B. V. D. No. 4 6-11-38	120 u. Ins. 5.8 c.c. Met.	116/50	96/28		-20	-22	+2	
	23	C. W. No. 13 5-21-38	30 u. Ins. 3 c.c. Met.	140/94	132/80		-8	-14	+6	
	24	C. W. No. 13 5-26-38	35 u. Ins. 3.2 c.c. Met.	112/68	116/66		+4	-2	+6	
	25	C. W. No. 13 5-28-38	30 u. Ins. 3.2 c.c. Met.	128/76	132/82		+4	+6	-2	
	26	C. W. No. 13 6-1-38	30 u. Ins. 3.2 c.c. Met.	118/76	126/72		+8	-4	+12	
	27	C. W. No. 13 6-6-38	30 u. Ins. 3.2 c.c. Met.	132/88	150/70		+18	-18	+36	
	28	C. W. No. 13 6-9-38	30 u. Ins. 3.4 c.c. Met.	122/78	120/72		-2	-6	+4	
	29	F. S. No. 8 5-25-38	140 u. Ins. 9 c.c. Met.	122/78	122/68		0	-10	+10	
	30	H. K. No. 12 6-11-38	15 u. Ins. 3.4 c.c. Met.	112/84	120/72		+8	-12	+20	

Range of Systolic B.P. Changes = -50 to +22; Average Syst. B.P. Change = -7.6; Average Syst. Change  $\bar{c}$  Excitement = -43.  
 Range of Diastolic B.P. Changes = -36 to +42; Average Diast. B.P. Change = -12.9; Average Diast. Change  $\bar{c}$  Excitement = -27.  
 Range of Pulse Pressure Changes = -52 to +52; Average Pulse Pressure Change = +4.9; Average P.P. Change  $\bar{c}$  Excitement = -16.5.  
 Number instances with obvious excitement = 4(+) (with excitement changes were always downward).

TABLE D  
EKG Effects of Metrazol

STATISTICAL DATA																					
Item No.		1		2		3		4		5											
Case No. Date of EKG		No. 1 W. B. 3-11-38		No. 2 E. D. 3-11-38		No. 4 B. V. D. 3-8-38		No. 5 W. C. 3-7-38		No. 6 M. B. 3-2-38											
Age of patient		46		41		26		41		38											
No. of previous metrazol treatments and fits		25 treatments 18 fits		25 treatments 14 fits		23 treatments 10 fits		7 treatments 4 fits		1 treatment 1 fit											
Dose of met. on date of EKG		10.2 c.c.		10.8 c.c.		12.6 c.c.		7 c.c.		4 c.c.											
EKG DATA: taken: (A) immediately before, and (B) within 10 minutes after Metrazol convulsion																					
EKG data		Before		After		Before		After		Before		After									
Rate		111		122		107		103		97		110		83		107		91		115	
Rhythm		Regular		Regular		Regular		† Grossly regular		Regular		Regular		Regular		Regular		Regular		Regular	
Duration of com-plexes (seconds)		P .08 PR .12 QRS .09 ST .22		.08 .12 .09 .20		.10 .20 .09 .24		.10 .19 .10 .26		.11 .17 .08 .24		.11 .17 .08 .20		.09 .14 .10 .24		.09 .14 .10 .22		.10 .18 .08 .22		.10 .18 .08 .24	

TABLE D—Continued

EKG DATA: taken: (A) immediately before, and (B) within 10 minutes after Metrazol convulsion	Amplitude of waves (in millimeters)									
	LEAD I	P <sub>1</sub> Q <sub>1</sub> R <sub>1</sub> S <sub>1</sub> T <sub>1</sub>	+ $\frac{1}{2}$ -1 $\frac{1}{2}$ +8 - +1	+ $\frac{1}{2}$ -1 +8 - +1	+1 - +2 -2 +1	+ $\frac{1}{2}$ - +2 -3 +1	+1 - +5 -2 +1 $\frac{1}{2}$	+1 -1 +6 $\frac{1}{2}$ - +1	+1 -1 $\frac{1}{2}$ +8 - +1 $\frac{1}{2}$	+1 -3 $\frac{1}{2}$ +10 $\frac{1}{2}$ - +1
LEAD II	P <sub>2</sub> Q <sub>2</sub> R <sub>2</sub> S <sub>2</sub> T <sub>2</sub>	+1 $\frac{1}{2}$ -1 $\frac{1}{2}$ +13 -2 $\frac{1}{2}$ +2	+2 - +13 -4 +2	+2 -1 $\frac{1}{2}$ +14 -2 +2 $\frac{1}{2}$	+2 -1 +12 -2 +1 $\frac{1}{2}$	+1 $\frac{1}{2}$ -2 $\frac{1}{2}$ +13 - +2	+1 $\frac{1}{2}$ - +12 -3 +1 $\frac{1}{2}$	+2 - +12 -3 +2 $\frac{1}{2}$	+1 $\frac{1}{2}$ - +12 -3 +2 $\frac{1}{2}$	+1 - +7 -2 +1
LEAD III	P <sub>3</sub> Q <sub>3</sub> R <sub>3</sub> S <sub>3</sub> T <sub>3</sub>	+1 $\frac{1}{2}$ -1 +13 -1 + $\frac{1}{2}$	+1 $\frac{1}{2}$ - +6 -6 +1	+1 $\frac{1}{2}$ -2 +17 - $\frac{1}{2}$ +1 $\frac{1}{2}$	+1 - $\frac{1}{2}$ +6 -1 Flat	Flat - +7 - + $\frac{1}{2}$	+1 - +9 - +1	+1 - +9 - +1	+1 - +9 - +1	+1 $\frac{1}{2}$ - +6 $\frac{1}{2}$ -1 $\frac{1}{2}$ +1 $\frac{1}{2}$
LEAD IV	P <sub>4</sub> Q <sub>4</sub> R <sub>4</sub> S <sub>4</sub> T <sub>4</sub>	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +
Cardiac apex to left leg	LEAD	P <sub>4</sub> Q <sub>4</sub> R <sub>4</sub> S <sub>4</sub> T <sub>4</sub>	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +	+1 - +2 $\frac{1}{2}$ -6 $\frac{1}{2}$ +

\* Occasional auricular extrasystoles after the fit. T<sub>4</sub> is -4 mm. or 2 mm. deeper after fit than before fit.† Occasional auricular and ventricular (left) extrasystoles are seen after the fit; T<sub>4</sub> is -4 mm. or 2 mm. deeper after fit than before.



TABLE D—Continued  
EKG Effects of Metrazol

STATISTICAL DATA	Item No.	6	7	8	9	10			
	Case No. Date of EKG	No. 7 M. C. 3-2-38	No. 3 H. T. 3-7-38	No. 3 H. T. 6-17-38	No. 3 H. T. 6-21-38	No. 14 R. M. 6-17-38			
	Age of patient	42	42	42	42	39			
	No. of previous metrazol treatments and fits	1 treatment 1 fit	23 treatments 16 fits	30 treatments 22 fits	32 treatments 23 fits	31 treatments 28 fits			
	Dose of met. on date of EKG	5 c.c.	9.6 c.c.	5.2 c.c.	6 c.c.	4.4 c.c.			
EKG DATA; taken: (A) immediately before, and (B) within 10 minutes after Metrazol convulsion	EKG data	Before	After	Before	After	Before	After		
	Rate	75	83	100	115	94	115	147	
	Rhythm	Regular	Regular	Regular	Regular	Regular	Regular	Regular	
	Duration of com-plexes (seconds)	P	.08	.09	.09	.09	.09	.09	.08
		PR	.15	.16	.13	.13	.14	.14	.12
	QRS	.09	.09	.06	.07	.06	.07	.06	
	ST	.26	.24	.28	.24	.28	.24	.26	

TABLE D—Continued

EKG DATA: taken: (A) immediately before, (B) 10 minutes after Metrazol convulsion	Amplitude of waves (in millimeters)									
	LEAD I	P <sub>1</sub> Q <sub>1</sub> R <sub>1</sub> S <sub>1</sub> T <sub>1</sub>	$\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$	Unsatisfactory graph (muscle currents)	$\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$	$\frac{1}{4}$ $\frac{1}{4}$ $\frac{1}{4}$ $\frac{1}{4}$ $\frac{1}{4}$	$\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$	$\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$	$\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$	$\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$
LEAD II	P <sub>2</sub> Q <sub>2</sub> R <sub>2</sub> S <sub>2</sub> T <sub>2</sub>	+1 — +9 —3 +2	+1 $\frac{1}{2}$ — +8 —3 +3	+2 — +10 —1 +1	+1 $\frac{1}{2}$ — +6 — +1 $\frac{1}{2}$	+1 — +7 — +1	+1 $\frac{1}{2}$ $\frac{1}{2}$ — — +1	+1 — +6 —1 +2	+1 — +7 — +2	+1 $\frac{1}{2}$ — +10 — +2
	P <sub>3</sub> Q <sub>3</sub> R <sub>3</sub> S <sub>3</sub> T <sub>3</sub>	+ $\frac{1}{2}$ — +2 $\frac{1}{2}$ —1 $\frac{1}{2}$ +	+1 — +1 —1 $\frac{1}{2}$ +	+1 $\frac{1}{2}$ — +7 — +1	+1 — +4 — +1	+1 — +4 — +1	+1 $\frac{1}{2}$ — +5 — +1	+1 $\frac{1}{2}$ — +5 — +1 $\frac{1}{2}$	+ $\frac{1}{2}$ — +5 — +1	+1 — +7 — +1
	P <sub>4</sub> Q <sub>4</sub> R <sub>4</sub> S <sub>4</sub> T <sub>4</sub>	+ $\frac{1}{2}$ — +2 —1 +	+1 — +2 —1 +	+1 — +2 —1 +	+1 — +2 —1 +	+1 — +2 —1 +	+1 — +2 —1 +	+1 — +2 —1 +	+1 — +2 —1 +	+1 — +2 —1 +
LEAD IV	Nothing abnormal	Nothing abnormal	Nothing abnormal	Not recorded	T <sub>4</sub> neg. shallow (—1 mm.)	T <sub>4</sub> diphasic — $\frac{1}{4}$ to + $\frac{1}{2}$	T <sub>4</sub> shallow (— $\frac{1}{2}$ mm.)	T <sub>4</sub> equals —2 mm.	Nothing abnormal	Nothing abnormal
	Cardiac apex to left leg	T <sub>4</sub> is —4 as compared to —3 mm. before fit	T <sub>4</sub> is —4 as compared to —3 mm. before fit		B.P. 135/72	Slight stimulation only B.P. 156/72		B.P. 118/44	B.P. 152/86	B.P. 148/78
Remarks										

\* Occasional auricular extrasystoles after the fit. T<sub>4</sub> is —4 mm. or 2 mm. deeper after fit than before fit.† Occasional auricular and ventricular (left) extrasystoles are seen after the fit; T<sub>4</sub> is —4 mm. or 2 mm. deeper after fit than before.

Similar differences are apparent as regards the diastolic and pulse pressure changes, and a similar, but even more marked trend, is discernible in table C<sub>2</sub> where the "metrazol with insulin" cases are listed.

The readings listed as item number 21 in table C<sub>1</sub> merit some special consideration. This patient, after this particular injection showed a drop of his diastolic blood pressure to zero, which persisted for several minutes. This is evidence of the appearance consequent to the seizure, of an adrenalin or adrenalin-mimetic effect, which is entirely similar to the adrenalin effect often obtained during insulin hypoglycemia. (This phenomenon has been fully described in our earlier paper<sup>10</sup>; its appearance as an effect of insulin hypoglycemia alone is illustrated by item number 15, in table C<sub>2</sub> and item number 5 in table B<sub>2</sub>.) This finding may be considered as confirmatory of our previous notations of the appearance of the aortic dilatation phenomena as described under the auscultatory findings. Additional evidence for such an interpretation of these findings will be presented in connection with the electrocardiographic studies. It must be reëmphasized that such evidences of adrenalin or adrenalin-mimetic cardiovascular activity were seen much less frequently and to a considerably lesser degree after metrazol injections than during insulin hypoglycemias. Patient H. T., on whom the readings listed as item number 21 were made, was one of those who had been particularly prone to exhibit the adrenalin-activity phenomena during his previous course of straight insulin treatment.

## II. ELECTROCARDIOGRAPHIC FINDINGS

Electrocardiograms were taken on eight of our more coöperative patients just before a metrazol injection and as soon as practical thereafter. This was done in 10 instances, in nine of which the desired result of a grand mal convulsion was obtained, while in one instance (item number 8) "slight stimulation only" was obtained. In the nine instances where a grand mal convulsion was obtained, the second electrocardiogram was taken as soon as possible after the last convulsive twitch, during the phase of postconvulsive coma. In the one instance where no convulsion was obtained, the second electrocardiogram was taken one and one-half minutes after the metrazol injection.

All of these patients had had electrocardiograms taken before the course of treatment was started as well as after it was finished. In addition, several of them had additional electrocardiograms taken during the afternoon or on rest days during the course of treatment. These data need not be presented here, because in no instance did there appear the slightest significant change, or evidence of cardiac damage as a result of the course of treatment. The temporary immediate changes contingent upon the individual metrazol injections are herewith presented in table D.

Analysis of the data listed in table D shows that there was no significant variation in the reaction in relation to the total number of treatments, or number of previous convulsions. The changes in rate were usually minor in


degree and confirmed the impressions previously noted by counting the pulse. In only two of the 10 instances (items number 9 and 10) did an acceleration of pulse of 32 to 42 per minute appear. The rhythm generally remained grossly regular after the fit—in one instance a slight sinus arrhythmia was noted, while in two cases occasional auricular extrasystoles appeared, and in one case rare ventricular extrasystoles were seen. There were absolutely no significant changes noted in the duration of the individual wave complexes. No significant variations were noted in the amplitude of the P, Q, R, or S waves, in any lead, except such slight increases in amplitude of the QRS complexes in two instances as might indicate a rather more vigorous ventricular action (see items number 4 and 10).

In no instances was there noted any significant deflection of the ST interval. The "T" waves generally showed either *no change* or a *slight increase* in amplitude ranging from  $\frac{1}{2}$  to 2 millimeters. This increase was generally in the direction of normality, so that  $T_1$ ,  $T_2$ , and  $T_3$  which are normally positive tended to become *more* positive, whereas  $T_4$  which is normally negative tended to become *more* negative. The change in the "T" waves was particularly evident in Lead IV (see items number 1, 2, 7, 9).

The only exceptions to this rule regarding the "T" wave changes are seen under items number 3, 4, and 8. Here we find "T" waves after the fit, which are slightly *diminished* in amplitude ( $-\frac{1}{2}$  millimeter) so that they may be considered *less* normal than before. The three cases on whom these graphs were taken were outstanding examples of those showing a special susceptibility of the cardiovascular apparatus to adrenalin or adrenalin-mimetic sympathetic activity as evidenced by aortic-dilatation phenomena, increased pulse pressure, vasomotor and pilomotor activity, when they had previously been treated with insulin.

## DISCUSSION

In seeking an explanation for the exceptional findings noted in a few instances above we are inevitably led to a consideration of the more recent literature regarding the physiology of epinephrine, at least as it affects the heart. In this regard Milles and Smith<sup>11</sup> have stated in substance: The intravenous injection of epinephrine causes electrocardiographic changes closely simulating those found in angina pectoris in which condition the myocardium but not the conduction mechanism is involved. A *wide variation* exists in the individual *susceptibility to the drug* in humans and in experimental animals. *The minimal effect is a reduction in amplitude of the "T" wave.* This is closely followed by the appearance of the diphasic form. Next directional changes in the T-wave appear, i.e., a previously upright T-wave becomes inverted or vice versa, or a marked increase in the voltage of the T-wave appears. Deviation of the ST interval is often associated with these pronounced T-wave changes. Finally ventricular extrasystoles and, with very large doses, ventricular fibrillation set in. With very large doses of epinephrine transient conduction interference may occur.



The work of Parade and Foerster<sup>12</sup> affords additional pertinent information as to the effect of epinephrine on the heart action. These investigators administered 0.015 mg. of a freshly prepared epinephrine solution intravenously to a series of 35 non-cardiac patients. They then took serial electrocardiograms in Lead II only, and in 18 cases observed definite rhythm changes which, however, always subsided within 5 minutes after the injection. The rhythm changes were divided as follows: nodal rhythm—five times; coronary vein sinus rhythm (an ectopic auricular rhythm)—two times; nodal extrasystoles—three times; auricular extrasystoles—four times; ventricular extrasystoles—three times. They also observed occasionally a slight sinus arrhythmia which was not due to respiration. In two cases they found rather long maintained deformities of the P-wave. In one patient there occurred an heterotopic auricular tachycardia. In almost half of their cases there occurred a slight fleeting shortening of the PR interval.

When we add to the above data our knowledge of the infrequently mentioned and rarely recognized clinical cardiovascular effects of hyperadrenalinemia (see number 10), namely the aortic dilatation phenomena, we find that we are able to formulate a reasonable hypothesis which will account for all the diverse clinical data disclosed by our study. First, we must recognize that individuals differ in the organization of their autonomic nervous system. This difference in autonomic organization is a most important factor of their general physical constitution or habitus. Consequently, they will differ in their response to various types of stimuli and, in the present connection, particularly in the degree of their response to drugs of the sympathetic-adrenal type. In other words, some individuals will show an increased, some a reduced, and some an "average" susceptibility or sensitivity to stimulation with adrenalin or sympathetico-mimetic drugs. Furthermore, it is now being recognized that the prolonged administration of insulin (as in the Sakel regime), may induce an altered state of reactivity of the sympathetic system, primarily in the direction of an increased sensitivity of response to adrenalin and sympathetico-mimetic drugs. On individuals with an "average" or "reduced" sensitivity of the sympathetic nervous system, it appears that metrazol, as at present employed, produces only minor cardiovascular effects, which effects correspond basically with the state of mental or emotional excitement produced by the action of the drug on the central nervous system. On the other hand, on patients with a hypersensitivity of the sympathetic nervous system, metrazol may produce, in addition, transitory effects which are typical of a mild hyperadrenalinemia, namely, aortic dilatation phenomena with reduced diastolic and increased pulse pressures, cardiac rhythm changes, and T-wave changes (such as were noted with patients H. T., W. C., and B. V. D.).

From the above formulation it follows that metrazol may logically be employed with safety in all cases which do not show definite evidence of serious organic heart disease. In cases of definite organic heart disease its use would seem to be contraindicated, when the disease is of a type which

tends towards permanent disturbances of rhythm (such as rheumatic, thyrotoxic, or advanced arteriosclerotic conditions), or of a type associated with defective coronary function (such as coronary sclerosis, or aortic regurgitation). In such cases, in sensitive or sensitized individuals, an injection of metrazol might conceivably induce sufficient additional sympathetic stimulation (or adrenalin secretion), to precipitate a cardiac accident. On the whole it appears that metrazol may be employed with a feeling of much greater assurance in borderline cardiac cases than would be the case with insulin, which, it has been shown, produces much more profound and more lasting changes in the cardiovascular physiologic processes.

Corresponding with the evident safety of metrazol as regards the cardiovascular apparatus, there appears to be no good evidence of its possessing any real value as a pure cardiac stimulant. It would seem that whatever good effects may be obtained from its use as a cardiac stimulant could best be explained by its pronounced respiratory stimulant action, with perhaps secondary improvement of cardiac function due to improved oxygenation.

#### SUMMARY

The present vogue of using massive doses of metrazol intravenously for the treatment of mental diseases, has afforded an unprecedented opportunity for studying directly the effects of this drug on the cardiovascular physiologic processes.

A survey of the current literature shows that there have been published comparatively few reports furnishing any specific data on this problem.

The present study lists changes in the physical signs, blood pressure, and electrocardiograms of 14 male patients receiving metrazol alone, as well as metrazol during the course of insulin hypoglycemia. It is indicated that there are no pronounced or prolonged alterations in blood pressure associated with the metrazol treatment per se, and that the changes which do occur reflect primarily the state of mental and emotional excitement or depression induced by the injection. It is also shown that the metrazol injections as a rule induce a *transitory* mild to moderate acceleration of cardiac rate (10 to 30 beats per minute), and at times *transitory cardiac irregularities* most often of the type of auricular extrasystoles, and sinus arrhythmia, with ventricular extrasystoles more rarely. We have not observed any instance of auricular fibrillation, although this has been reported by another investigator (Haddon). It is also shown that patients who are "sensitive" or "have been sensitized" (by previous treatment with insulin) may show temporary signs of aortic dilatation phenomena, analogous to the known effects of a mild hyper-adrenalinemia. Except in such "sensitized" patients, where the electrocardiograms may indicate a slight tendency towards diminished coronary oxygenation, the electrocardiograms after convulsions invariably indicate either no change or improved coronary oxygenation, associated with the more vigorous heart action. The theoretical implications of these findings

are suggested and the relative safety of metrazol treatment as regards improbability of cardiac complications is stressed.

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# ACTINOMYCOSIS: A NEW SPECIES, PATHOGENIC FOR MAN \*

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THE diagnosis of human actinomycosis is not always made with ease, and furthermore the identification of the causative species is usually quite difficult. In medical literature cases are frequently reported as actinomycosis followed by the statement, *unable to culture, culture lost, not able to identify*, etc. The species in some cases is not of great interest to the physician; however, the laboratory should always attempt to identify the organism.

The disease may be either localized or generalized. It is usually chronic and the duration is from several months to several years. It is thus frequently misdiagnosed "tuberculosis."

In 1925, Sanford and Voelker<sup>1</sup> reviewed 670 cases that had been observed up to that year in the United States, and of these only 2 per cent showed generalized involvement. Brumpt states that in those infections caused by *A. israeli*, the etiological agent of lumpy jaw in cattle, 60 per cent of the cases are of the cervico-facial type. When all causative species are grouped together this percentage is much greater. In certain cases decaying teeth may contain the organism and as such may be the source of the infection. Topley and Wilson<sup>2</sup> state that *A. graminis Bostroem* is occasionally present in actinomycotic lesions and is probably not etiologically related to the disease. This organism, like the one herein later described, has been found in the mouth.

Some of the many difficulties and peculiarities encountered in the study of the group are: (1) their minute size and variation in morphology on various media; the difficulty of studying the morphology unless the highest magnifications are available, that is about 2700; (2) extreme variability of growth on synthetic media; (3) uniformity of growth on protein media; (4) the presence or absence of diffusible pigments, the colors of which may change with a variation in the pH; (5) sensitivity to an acid medium; (6) formation of zones of peculiar designs on media; (7) possible loss, after several transplants, of some of the characteristics by which they are identified. (Some of these characteristics may be regained by cultivation in media containing sterile soil, for the original source of this fungus is the soil.)

There are many species more or less pathogenic to man and animals. Brumpt<sup>3</sup> lists over one hundred. Dodge<sup>4</sup> lists about the same number. In many, pathogenicity has not been proved. Different species have been isolated from infections of the tear ducts, cornea, conjunctiva and tongue. They have been found in decaying teeth, in the sputum, in the lungs, in the spleen, and in chronic abscesses in various parts of the body. Other species

\* Received for publication July 9, 1938.

† Deceased.



have been frequently reported in chronic bronchitis and also as associated with the tubercle bacillus in the sputum. In rarer instances we find actinomyces reported in brain abscesses, granulomas, skin mycosis, keratolysis of the skin of the feet in India, and in the blood stream of persons bitten by certain small wild animals. It is well known that several species are the etiological agents of Mycetoma or Madura foot. Generalized actinomycosis caused by the *Actinomyces bovis* of Hartz has been extensively studied by several investigators. The physician's knowledge of the disease and the organism has been largely limited to this species.

#### CASE REPORT

*Clinical History:* V. B., white male, aged 41 years, was first seen December 21, 1935, when he complained of dental pain in the lower right jaw. Examination at the Dental Clinic, Fort Leavenworth, Kansas, showed caries with periapical abscess of

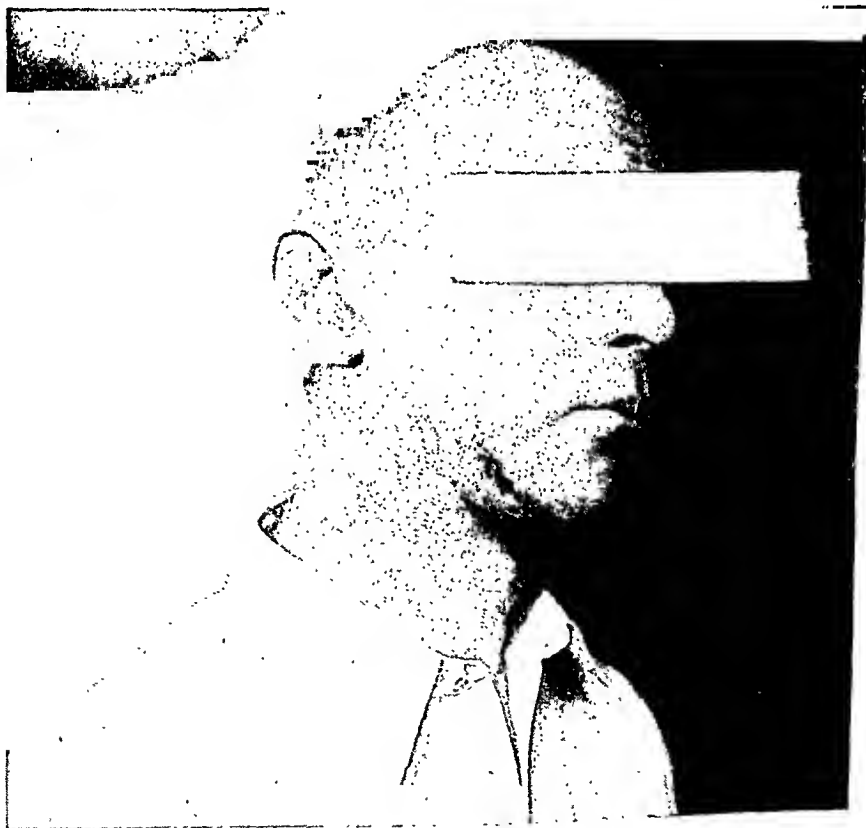


FIG. 1. The lesion.

the right lower, first and second molars, pulpitis of the left lower second bicuspid and periodontoclasia of the left lower second molar. The abscesses were drained, and a few days later fluctuation appeared midway along the lower line of the right mandible. This was excised and drained. The two abscessed teeth were removed on January 3 and 6. The wound in the gum healed readily but the external wound would not close; fluctuation would again start in an adjacent indurated area. When the latter area was incised and drained, it would close and the process would begin anew.

The patient was admitted to the Station Hospital, Fort Leavenworth, on February 17, 1936, two months after the first complaint, that of dental pain. He was admitted for treatment of the abscessed area of the right lower jaw, which had become quite extensive and had become tender to light pressure.

*General Physical Examination:* This was essentially negative and remained so throughout his stay in the hospital.

*Progress in the Hospital:* The temperature was normal and remained so during the entire course of the illness. The wound was kept widely opened, and was packed

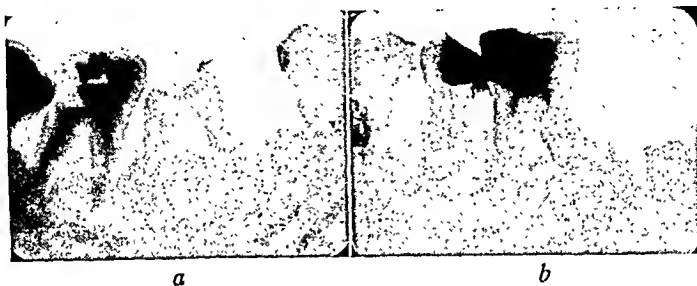


FIG. 2a. Dental—right first and second molars.  
2b. Dental—left first molar.

and dressed daily. The pus was a thick yellow but it became thin and watery as the wound closed, only to indurate again and break down repeatedly, as it had done prior to admission. The cervical glands were not enlarged. Fungus infection had been suspected by the surgeon for some time, but the laboratory findings were always negative, i.e., the bi-polar staining bacillary forms were not recognized as fungus. Potassium iodide was begun on March 2, a week before fungus was reported. The initial dose of 10 drops of saturated solution t.i.d. was gradually increased to 78 drops t.i.d. In addition roentgen-ray treatment was given once weekly. The wound showed much stubbornness in healing, but it finally cleared up completely except for a considerable amount of scarring. The patient was discharged on May 16, 1936.

*Laboratory Findings during Time the Patient Was in the Hospital:* On February 20, smears from the discharge were reported to contain diphtheroid-like bacilli, streptococcus and staphylococcus. Repeated cultures taken during the next two weeks continued to show the same organisms. The roentgen-ray report was negative for osteomyelitis. Blood culture taken February 19 was negative. On March 9, thread-like fungi were reported in smears, for the first time. They were aerobic, gram-positive and not acid fast. The same organism was reported on March 18 and 19. In the pus were noted minute, pale yellow, soft granules. These when crushed and stained showed colonies of actinomyces.

*Histopathology:* Tissue from the wound was sent to the Army Medical School. The report received March 15 was "chronic inflammation and small coccoid forms." Six guinea pigs were inoculated intraperitoneally with both exudate and broth cultures. In 10 days all showed small nodules at the site of inoculation. At the end of four weeks, in two of the animals nodules were found in the peritoneum and omentum. Actinomyces of the same type as herein described were cultured therefrom. In our work we were unable to confirm this finding. The remaining four pigs were kept for two more months, during which time they appeared normal.

On April 3, smears and cultures were finally diagnosed as *Actinomyces*, probably *graminis*. On April 10, pus from the jaw wound showed a few branching fungi on smear and in culture. There were many negative reports between February 17 and April 10. Blood count: On only one occasion, March 13, was this abnormal: white

cells 14,700 with 70 per cent polymorphonuclear cells. Red count and differential normal. Wassermann and Kahn reactions negative. Cultures were not taken from the teeth because they were removed before the actinomyces was suspected, and before the patient had been admitted to the hospital.

COMMENT: In this case of localized actinomycosis we wish to call attention to the following points:

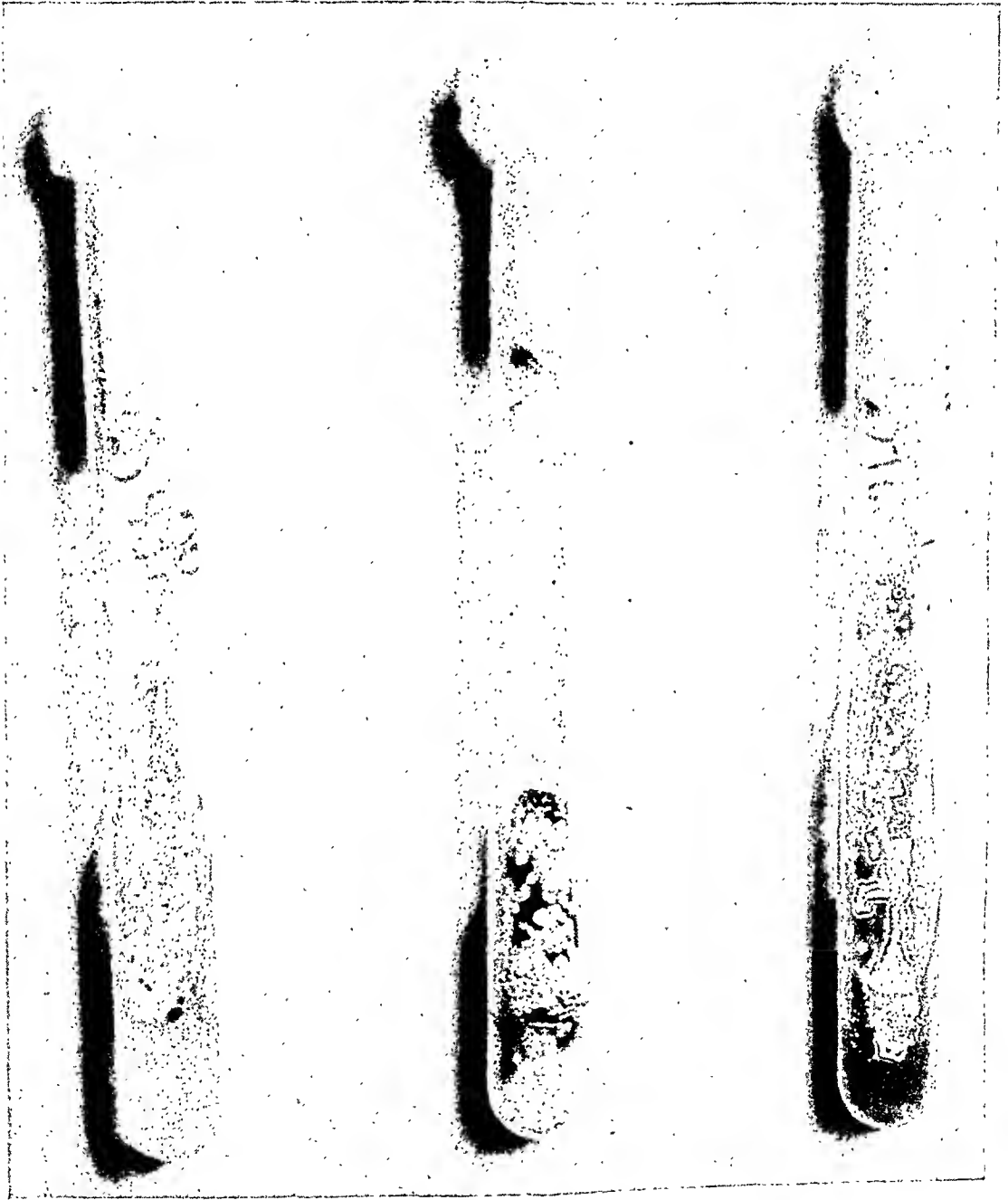


FIG. 3. The cultures showing interesting designs which may be characteristic. Left: asparagus, twelfth day. Middle: potato, twelfth day. Right: starch, twelfth day.

1. The abscess was not along a definite chain of glands as in tuberculosis.
2. Actinomycosis should always be suspected, especially in the cervico-facial area, when an abscess refuses to heal under appropriate local treatment, and the complement fixation and tuberculin tests are negative.
3. It is probable that had the organism invaded the blood stream abscesses would have occurred elsewhere and the disease might have become generalized.
4. A few weeks' delay in diagnosis may be fatal.
5. In the tissue and cultures various species of actinomyces may show coccoid, rod forms, and diphtheroid-like forms.
6. In the pus, sulphur-like granules are not always found. The same holds true for the material from the curettage of a sinus. All species do not show these granules which are characteristic of *Actinomyces bovis*.
7. The adjacent glands may not be involved.
8. The condition may be confused with tuberculosis and osteomyelitis.
9. The importance of an early localized actinomycotic infection should not be overlooked. It may become generalized.
10. Cultures should be studied for at least four weeks to determine if segmentation is present. It is often necessary to make a prolonged search for branching forms.

#### DESCRIPTION OF THE ORGANISM

Shortly after the writer came to this laboratory in May 1937, he found cultures of this actinomyces. The clinical technician, Miss Pearl Moorman, who had first recognized the filaments, described the case in such an interesting way that it was decided to attempt an identification.

On October 24, 1937, the following aerobic protein cultures were planted from old cultures dated May 18, 1936. These blood agar slants appeared to be about 70 per cent dried out. Transplants were made from a few whitish specks on the surface but were not successful. However, after admitting air the chalky white specks increased in number, and growth was obtained. The following protein and vegetable cultures were incubated at 36° C. for six days—then maintained at 18° to 22° C.

1. Rabbit blood agar slants. Period at 36° C. In 48 hours the slant was covered with heaped up, chalk-like, white, dry, finely wrinkled, confluent colonies. Hemolysis extended 10 mm. from the edge of the confluent colonies and 2 to 3 mm. from the edge of individual colonies. A similar transplant made at the same time on the same medium showed in 48 hours at 36° C. a number of discrete grayish white, glistening caput-like colonies, 4 by 4 mm., with distinct fimbriated borders which in 76 hours were covered with the same chalky substance as noted in the first transplant, and hemolysis of the slant was nearly complete. Fifth day: Growth rapid, abundant, elevated, confluent, dry, chalky with distinct contour lines, some

roundish, others squarish (see photographs). The margin was narrow, crenated and transparent in places. Growth was attached to the medium but the whitish substance was easily detached. Hemolysis was almost complete, butt excepted. One of the blood agar slants did not show the contour lines distinctly. Thirtieth day: Color had gradually changed to grayish white. Contour lines remained. Edge was lobate with shrinkage in the center of growth and the surface finely pitted, but still remained dry and powdery. Short aerial mycelium, no soluble pigment.

2. Glycerol agar slant: pH 7.2. Good rapid growth similar to above. Pattern not as distinct, more pitting of surface which is velvety and glistening with edge erose.

3. Glucose agar shake: Growth only on surface with faint blackish brown coloration a few millimeters below the surface. It is probable that this color is due to the oxidation of the glucose.

4. Glucose agar slant: Good growth, similar to number two above, but with blackish brown color diffusing into medium for a few millimeters as in number three above.

5. Loeffler slant: Rapid liquefaction which began in 40 hours and continued to about 50 per cent on the fifth day:

6. Glycerol egg slant: Liquefaction rapid.

7. Litmus milk: No typical acid coagulation. A soft jelly-like thickening with liquefaction beginning on the third day. Remained alkaline. In 10 days 60 per cent digestion.

8. Sabouraud's conservation agar: Growth similar to other solid media but not as heavy.

9. Nutrient broth, pH 6.8: Pellicle and bottom growth heavy on fifth day. Medium clear. Growth flaky, membranous and granular, depending on position in the tube. Growth up around sides of the tube above the surface. Mycelium and coccoid forms.

10. Plain agar slant: Abundant rapid growth, similar to other solid media. On filling tube with water the appearance of growth is that of a shining silver-like molten metal. No pigment. Short aerial mycelium.

11. Sabouraud slant, 4 per cent maltose, pH 6.2: Abundant and rapidly growing confluent growth, raised, buff colored, dull, coarse white granules over part of surface. Contoured border distinct and crenated with whitish stellate projections. Reverse brownish black, burnt sugar color.

12. Carrot slant: Good confluent growth. Color whitish with areas of dirty yellowish brown, mottled by a darker brown along sides of surface growth.

13. Glycerol potato slant: Growth rapid. Second day: Thin yellowish growth, borders white becoming heavy grayish white and yellow. In 10 days, heavy incrustations of chalky white substance which after 30 days becomes grayish and somewhat greenish at the base where in contact with glycerol cotton plug. Spore-like and diphtheroid-like forms. Short mycelium grows readily from the surface.

14. Gelatin: Rapid stratiform liquefaction. Synthetic media. Incubated at 36° C. for 24 hours, then maintained at 27° C.

15. Asparagin slant: Fourth day: Heavy grayish white growth on surface. Border fine and fuzzy. No diffusing pigment. Seventh day: More yellowish and drier. A few individual colonies, 2 mm. in diameter with an acuminate center growth pitted and circumscribed by a fine line of growth, a Saturnine-like ring with a clear space within. Many fine white, dust-like particles. Border finely fuzzy. Reverse a faint greenish yellow.

16. Citrate agar slant: Fourth day: Very faint colorless growth along streak. Seventh day: A dozen white powdery points less than 1 mm. in diameter. No pigment. Growth poor.

17. Starch slant with brom-cresol purple: Fourth day: Similar to asparagin but not as heavy. Seventh day: No reverse color, no liquefaction, no pigment. Growth more rapid, becoming confluent and taking on a pattern (see photographs). Short aerial mycelium. Very faint change in reaction.

18. Czapek agar slant: Fourth day: Acuminate white colonies, black speckled along streak, fir tree-like. No pigment, does not spread into medium. Aerial mycelium not noted. In 10 days many minute colonies fusing here and there. In the synthetic media no further change other than increase in growth noted between seventh and fifteenth days.

*Biochemical Characteristics:* Glucose, maltose, lactose, salicin, seven days, no change. Indol, methyl red, V.P., methyl blue reduction test, all negative. Nitrates reduced to nitrites.  $\text{NH}_3$  positive; catalase positive, rapid. Microscopic: Branched filaments about one micron in diameter, some of which contain many granules in terminal elements, probably spores. No spirals seen. Chalky surface growth is made up largely of spore-like forms, 1 or 2 microns in size which appear in short chains like streptococcus. Microcultures of these develop hyphae over night. Gram positive, not acid fast.

*Animal Inoculations:* A guinea pig and a rabbit were inoculated intraperitoneally and two similar animals subcutaneously with 1 c.c. of culture suspension. None of them lost weight or presented any abnormal signs at any time. At five weeks the first two above mentioned were opened and no pathological condition found. The remaining two are healthy and gaining weight. Actinomyces as a rule are not very pathogenic for laboratory animals.

## DISCUSSION

After many months of work we are not able to correlate this organism with any known species. Knowing that some actinomyces change their characteristics on repeated subculture, we were careful to note that this species has retained all of its original properties, as far as we can determine from the records available. The works of various authors as Bergey,<sup>5</sup>

Topley and Wilson,<sup>6</sup> Dodge,<sup>7</sup> Brumpt,<sup>8</sup> and Waksman<sup>9</sup> have been consulted. We have written others but they have been unable to assist us. Waksman, in a personal communication, after a study of the culture sent him, says it "corresponds very closely to *A. hominis* Bostroem, which is the same as *A. gramineae*, Topley and Wilson." However, he does state that the proteolytic and diastatic properties of our organism differ from the above. The following table will show the different characters of the two species:

Media	<i>A. graminis</i>	<i>Actinomyces</i> sp. nov.
Gelatine	Liquefaction unusual.	Rapid liquefaction.
Broth	Pinkish, yellowish or orange in color. No odor.	None but chalky white. Odor distinctive.
Glucose agar slant	At three weeks, brick red or yellowish orange.	No such color. Blackish color below surface diffusing a few millimeters into medium.
Loeffler's serum	No liquefaction 24 days.	Rapid liquefaction.
Egg slant	No liquefaction 24 days.	Rapid liquefaction.
Blood agar slant	No hemolysin (Topley and Wilson). Hemolytic zone (Waksman).	Rapid and early hemolysis.
Czapek agar	Becoming yellow and brown as it dries. Penetrates the medium.	Fine white, black speckled colonies along streak. Does not penetrate into medium. Later brownish.
Starch	Enzymatic zone 12-16 mm.	No enzymatic action.
Odor	None mentioned.	Heavy penetrating, moldy, escaping through tube plugs.

This comparative table shows beyond a doubt that on a physiological basis the two actinomyces are not the same. One is not even a variety of the other, but both are distinct species.

### CONCLUSION

1. The organism described is a new species. We propose to call it *Actinomyces Moormani* after the technician herein previously mentioned because she was the first to differentiate it from a cornyobacterium.
2. It is pathogenic to man, forming chronic abscesses.
3. Like *A. graminis* it is probably found in the mouth as a saprophyte.
4. For the purpose of identification of an actinomyces it is suggested that the media and procedures mentioned herein are all necessary and useful.

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## THE PATHOGENESIS OF HEMORRHAGE IN ARTIFICIALLY INDUCED FEVER\*

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ARTIFICIALLY induced fever has attained a definite place among modern therapeutic procedures. Hyperpyrexia, however, is attended by actual, as well as by potential dangers, as is usually the case with any powerful therapeutic agent. Tissue injury from prolonged or excessive exposure to heat has long been recognized. Two of the most constant pathologic findings under such circumstances have been acute liver damage and hemorrhage. In replies to a questionnaire regarding fever therapy, which was sent to physicians by the Council on Physical Therapy, "several reported instances of cerebral hemorrhage."<sup>1</sup> Five fatalities have been cited by Härtman and Major<sup>2, 3</sup> and Wilbur and Stevens.<sup>4</sup> Necropsy findings included liver necrosis, hemorrhagic pneumonia, hemorrhagic encephalitis involving the vessels at the base of the brain, subconjunctival hemorrhages, submucosal hemorrhages in the trachea, and subendocardial and myocardial hemorrhage.

Pathologic findings in experimental animals subjected to artificial fever by various means have been reported by Baldwin and Nelson,<sup>5</sup> Hall and Wakefield,<sup>6</sup> Hargraves and Doan,<sup>7</sup> Hartman and Major,<sup>2, 8</sup> Jacobsen and Hosoi,<sup>8</sup> Mortimer,<sup>9</sup> and von Haam and Frost.<sup>10</sup> Hemorrhages have been reported in each instance. These included hemorrhage into the bone marrow, lymph nodes and splenic pulp, cortex and medulla of the brain, cortex of the adrenal gland, subpericardium and valves of the heart and extravasation of blood into the submucosa and subserosa of the intestines. Liver damage was reported in most instances. Jacobsen and Hosoi found changes in the peripheral zone of the liver lobules and fatty damage to the parenchymatous cells. Hall and Wakefield stated that the initial liver damage was central and "of a milder degree than the necrosis found in acute yellow atrophy." Engorgement of the sinuses, extensive midzone necrosis and hemorrhage into the liver substance were reported by Hartman and Major.

The etiologic mechanism of the hemorrhages invoked by fever has never been entirely satisfactorily explained. Wilbur and Stevens<sup>4</sup> stated that hemorrhage might be due to extreme dilatation of the vessels which allowed extravasation of the red cells, or, possibly, that it was the result of capillary damage not demonstrated anatomically; the liver damage they hypothesized as the direct result of actual heat or as secondary to intoxication. Hartman<sup>2</sup> noted the similarity between the pathologic lesions following fever therapy and those due to prolonged asphyxia in acute alcoholism, carbon monoxide

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or nitrous oxide poisoning. A constant and severe anoxia was demonstrated in experimental animals following induced fever as a result of decreased oxygen saturation of the arterial blood and a low oxygen content of the venous blood. Factors contributing to the anoxia were alkalosis, accelerated blood flow, the increased temperature of the blood and an increased demand for oxygen by the tissues.

Prothrombin, fibrinogen and blood platelets are among the more important known factors essential to the coagulation of blood, and are the products of organs proved to be affected pathologically by high fever temperatures.<sup>11, 12</sup> Prothrombin and fibrinogen are produced in the liver, and platelets arise from the megakaryocytes found principally in the bone marrow.<sup>13</sup> The hemorrhagic diathesis in thrombocytopenic states is well recognized. Hemorrhage may also occur when the prothrombin level falls to below 40 per cent of normal values.<sup>14</sup> Deficiency in prothrombin can be quantitatively determined by the methods of Smith, Warner and Brinkhous,<sup>15, 16</sup> and Quick, Stanley-Brown and Bancroft.<sup>17, 18, 19</sup> These investigators have reported a decrease in prothrombin levels associated with liver damage. More extensive liver necrosis must be present before there is a pathologic decrease in fibrinogen. Smith, Warner and Brinkhous<sup>16</sup> have shown that it is possible to decrease the prothrombin and maintain the fibrinogen level with carefully adjusted amounts of chloroform, a toxic hepatic agent. Larger amounts of chloroform result in a decrease of both factors.

The present study was undertaken to explore further into the underlying mechanism of the hemorrhagic tendency accompanying fever. The icterus index, liver function studies, prothrombin values and fibrinogen determinations were obtained to determine the relative efficiency of the various hepatic functions, and more particularly to detect any significant variation in the products of hepatic origin that are important in the coagulation of blood. Parallel determinations of circulating blood platelets and serial bone marrow biopsies were done. Observations on the number and character of the megakaryocytes were correlated with the level of the platelets in the peripheral blood.

#### METHODS

The method of Quick, Stanley-Brown and Bancroft<sup>17, 18, 19</sup> for prothrombin was used in human patients. This technic proved unsatisfactory for accurate quantitative prothrombin determinations using rabbit plasma. A modification of the method of Quick was devised. Blood from the heart was obtained and mixed with one-tenth its volume of sodium oxalate. The hematocrit and total volume were recorded after centrifugalization. A series of 10 dilutions in saline from 10 per cent to 100 per cent was prepared. Two drops of thromboplastin were added to two drops of each dilution. To this mixture were added four drops of calcium and fibrinogen solution, and the clotting time at 37° C. was recorded. The dilution which clotted in 20 seconds was noted and compared with a known normal plasma. Thus, if a

20 per cent solution of normal plasma clotted in 20 seconds, and a 30 per cent solution of the unknown plasma clotted in 20 seconds, the latter would be 10 per cent less or 90 per cent of normal. By this method rabbit plasma contained about 90 per cent and human plasma about 80 per cent as much prothrombin as dog plasma, which results are comparable to those reported by Smith, Warner and Brinkhous.<sup>14, 15, 16</sup> The method developed by Smith, Warner and Brinkhous is now being used in our laboratory.

The newer method of Greenburg and Mirolubova<sup>20</sup> with the modification suggested by Minot and Keller<sup>21</sup> has been found entirely satisfactory for the quantitation of fibrinogen.

As a further measure of liver function, the standard galactose tolerance and hippuric acid tests have been used in all human case studies. The bromsulphalein test was used giving five milligrams of the dye intravenously for each kilogram of body weight.

In the clinical studies, the sternal puncture aspiration technic was used for obtaining marrow. A different rib interspace was selected for each subsequent observation. Total cell counts were obtained with the standard pipettes and diluting fluids used in peripheral blood studies. The total nucleated cell counts were slightly lower than those reported by Erf.<sup>22</sup> The marrow tissue was studied immediately in supravitaly stained preparations with differential cell counts, and fixed films were made for Wright's Giemsa staining. The remaining material was allowed to clot, was fixed in Helly's fluid, embedded, and paraffin sections were stained with eosin and hematoxylin.

In rabbits, a preliminary aspiration biopsy of the femur marrow and tissues obtained immediately post mortem were studied by the above methods. Because of the dense cellularity of the rabbits' marrow, accurate total counts were impossible to secure, but differential counts and qualitative changes in the cells were recorded in each instance.

In human subjects the indirect method of Dameshek<sup>23</sup> was used for platelet determinations. Normal counts range between 400,000 and 700,000 per cubic millimeter of blood.

In rabbits a modification of the method of Olef<sup>24</sup> using Dameshek fluid was employed. An area of the ear vein was covered with vaseline and punctured through a drop of fluid preservative. The blood and dye solutions were transferred to a paraffin cup and thoroughly mixed. The film preparations were then made as in the human subjects.

#### OBSERVATIONS UNDER EXPERIMENTAL CONDITIONS

Rabbits were used as experimental animals, fever being induced by radiotherm. No barbiturates or narcotics were used. An individual difference in the susceptibility of the several coagulation factors to fever temperatures was noted in the various animals. During and following artificially induced hyperthermia, there was a decrease in total platelets in all instances, the

lowest determinations being one-fourth to one-third of the pre-fever control values. More or less extensive megakaryocytic damage was apparent during the period of low peripheral platelet values and a prompt and rapid regeneration of new megakaryocytes in the marrow always preceded the return of the circulating platelets to normal levels. A quantitative decrease in prothrombin and fibrinogen occurred in those animals in which liver damage was later found, and where no hepatic damage could be demonstrated, no disturbance in prothrombin had been recorded.

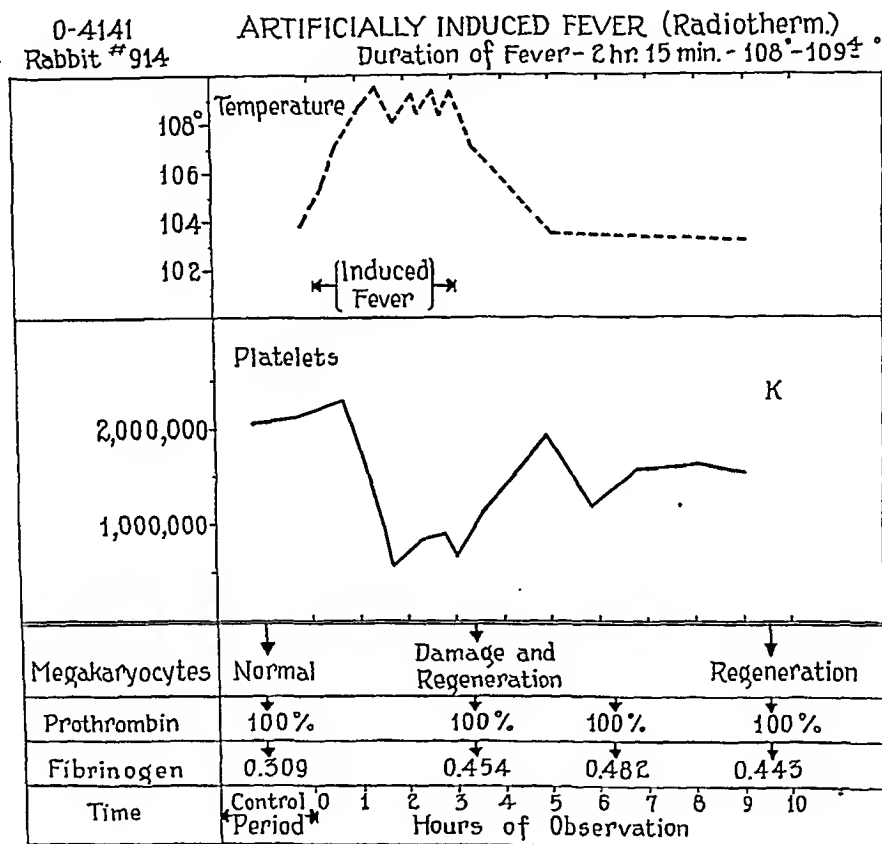
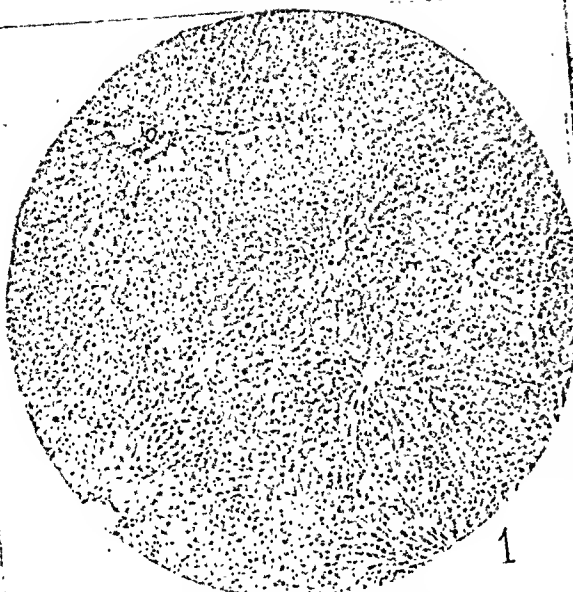
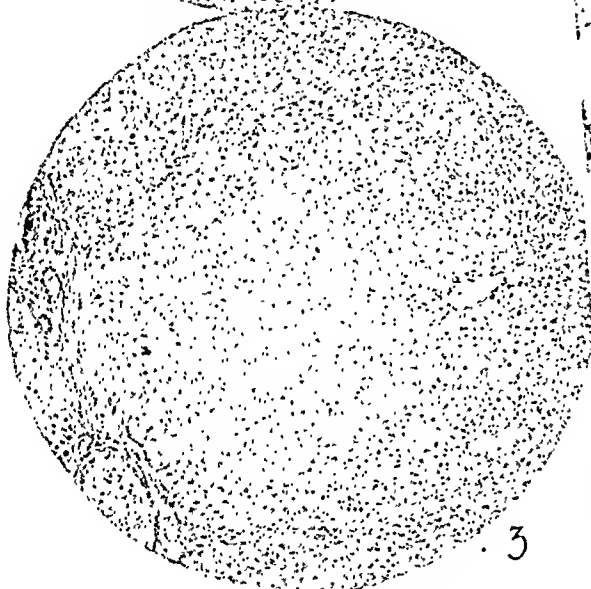


CHART 1.

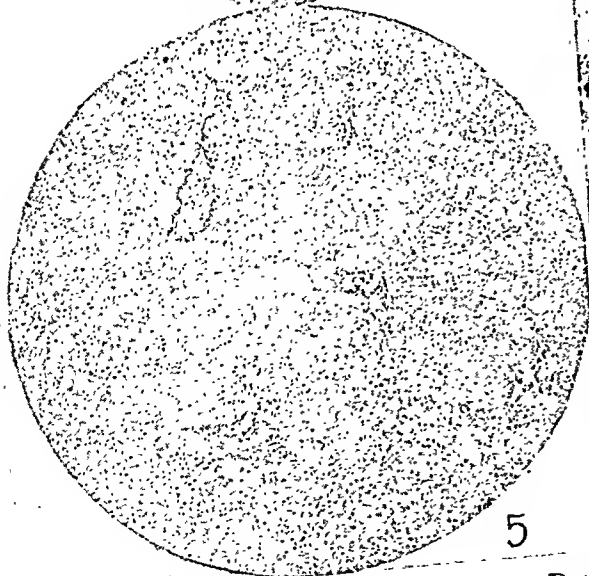
The first rabbit (chart 1) which received two hours and 15 minutes of fever between 108° and 109.4° F., showed a depression in only one of the coagulation factors as a result of hyperpyrexia. During the induction of fever there was an elevation in the platelet level, following which there was a steady decrease to about one-fourth of the control values. The platelets remained at this low level until after the radiotherm induction was discontinued and then gradually rose to slightly below the pre-fever level. There was no quantitative change in either prothrombin or fibrinogen. At necropsy there was no evidence of hemorrhage, either grossly or microscopically. Examination of the bone marrow (plate 1, figure 2) revealed both normal and



1



3



5



4

6

injured megakaryocytes with pyknotic nuclei. There were also young regenerating megakaryocytes. The liver cells were normal (plate 1, figure 1).

A quantitative decrease in platelets, prothrombin and fibrinogen occurred in the second rabbit, febrile for two hours with a gradual increase to

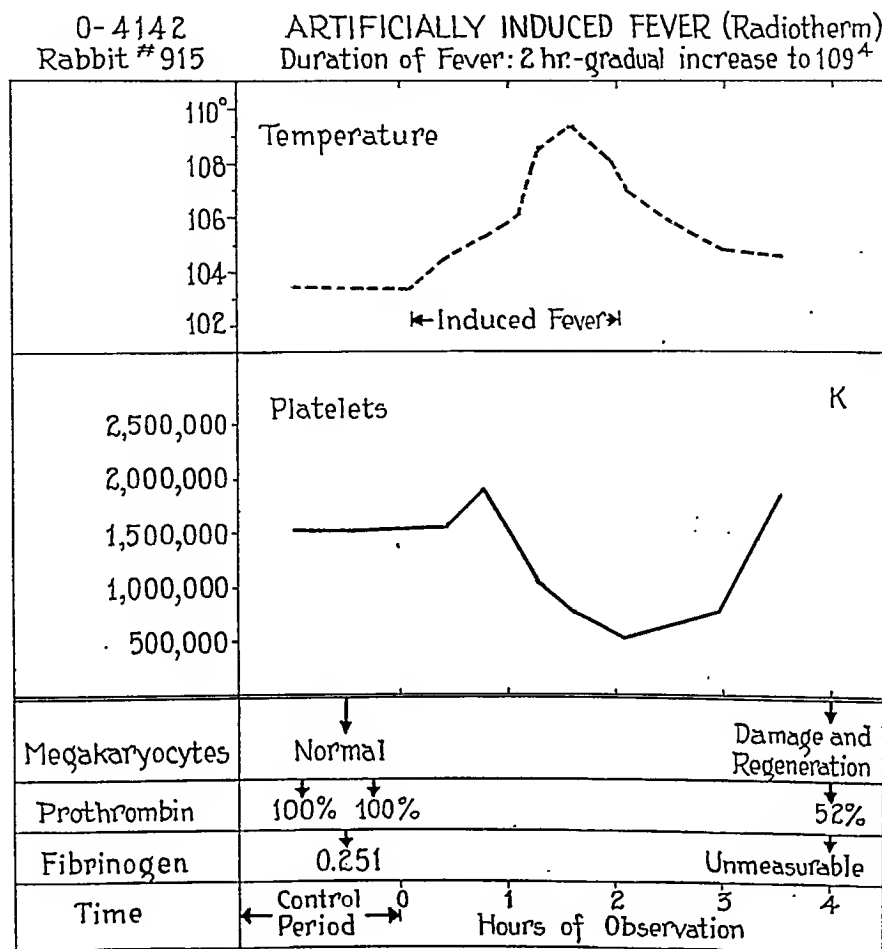


CHART 2.

$109.4^{\circ}$  F. (chart 2). Early in the period of induction of fever there was again a slight elevation in the platelet level, after which there was a decrease to about one-third of the control level. After the fever was discontinued the platelets returned rapidly to slightly above the pre-fever level. The pro-

PLATE I. Microscopic sections of liver and bone marrow after artificially induced fever.

FIGS. 1 and 2. Rabbit 0-4141. Duration of fever  $2\frac{1}{2}$  hours, temperature  $108-109.4^{\circ}$  F. The liver cells are normal. There are both normal and damaged megakaryocytes with pyknotic nuclei in the bone marrow. See Chart 1.

FIGS. 3 and 4. Rabbit 0-4142. Duration of fever 2 hours, highest temperature  $109.4^{\circ}$  F. The liver shows some degeneration of the cells in the periphery of the lobule, the cells in the central zone being filled with glycogen. The marrow shows mature normal, damaged, and young regenerating megakaryocytes. See Chart 2.

FIGS. 5 and 6. Rabbit 0-4143. Duration of fever 2 hours, lethal temperature  $111^{\circ}$  F. Both the liver and the marrow show acute cellular degeneration. The megakaryocytes are distinctly damaged. See Chart 3.

thrombin fell to 52 per cent of normal post-fever. An accurate fibrinogen quantitation could not be made due to the fragility of the fibrin clot. The bone marrow was examined after the animal was sacrificed, and there were normal, mature, damaged, and young regenerating megakaryocytes found side by side (plate 1, figure 4). The liver showed degeneration of the cells in the periphery of the lobule, the cells in the central zone being filled with glycogen (plate 1, figure 3). Small punctate hemorrhages were seen grossly

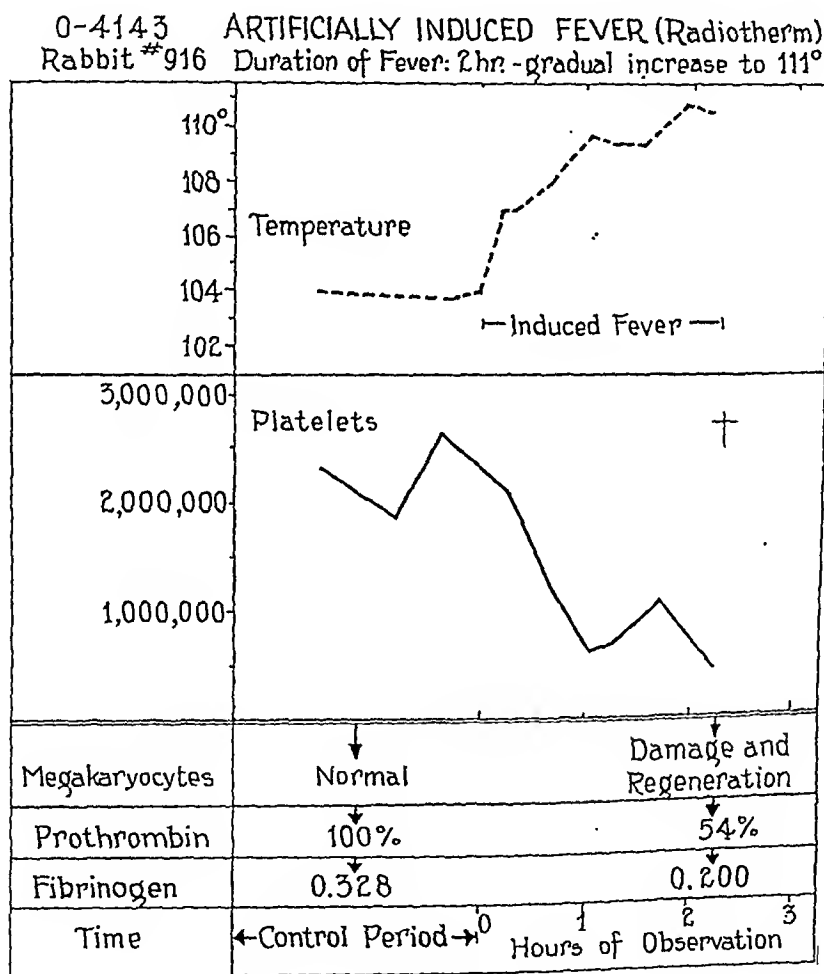


CHART 3.

in the lymph nodes, thymus and bone marrow. Microscopic examination revealed an early hemorrhagic pneumonia.

Fever induction was lethal after a gradual increase to 111.0° F. in two hours in the third rabbit (chart 3). There was a continuous fall in the platelet level, and the prothrombin immediately before the death of the animal had decreased to 54 per cent of normal. There was a similar decrease in the fibrinogen. Examination of the bone marrow revealed nuclear damage to the majority of the mature megakaryocytes, although a beginning regeneration of very young cells could be seen (plate 1, figure 6). Micro-

scopic examination of the liver revealed acute cellular degeneration (plate 1, figure 5). There was gross hemorrhage into the substance of the lymph nodes. Small punctate hemorrhages were grossly visible in the thymus. Microscopic examination revealed an early hemorrhagic pneumonia and small focal hemorrhages and swollen hemorrhagic glomeruli in the kidney.

## OBSERVATIONS IN HUMAN DISEASE

The patients selected for this study were all young adult individuals, normal to complete physical and laboratory examinations except for some type of gonorrheal infection. The galactose tolerance, hippuric acid and brom-

0-4036 C.H. ♀  
Aged 20 years.

FEVER THERAPY - 1st. Treatment  
Duration of Fever:  $106^{\circ}-107^{\circ}=9\text{ hr.}$ ;  $104^{\circ}-107^{\circ}=10\text{ hr. } 30\text{ min.}$   
G.C. Arthritis

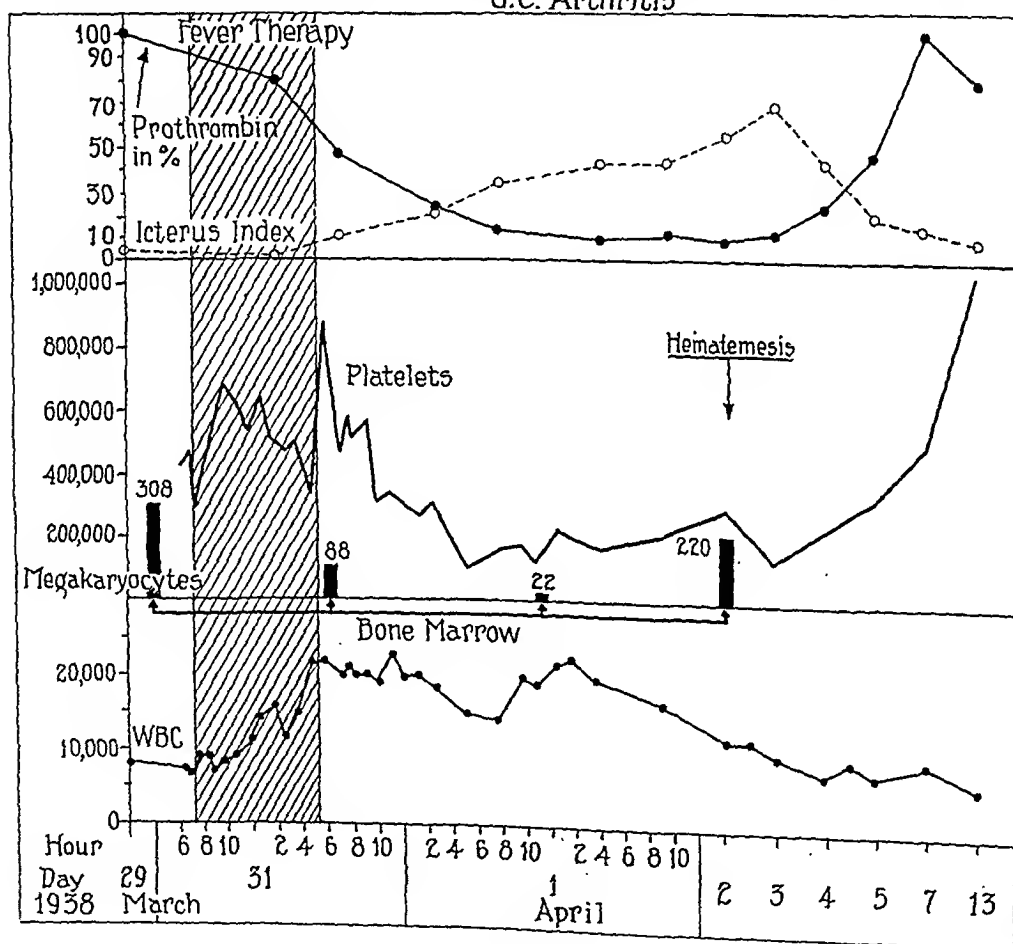


CHART 4.

sulphalein dye tests were normal before therapy in each individual. Only the bromsulphalein dye test could be repeated satisfactorily post-fever because of nausea and vomiting. Artificial fever was induced by the Kettering hypertherm. As in the experimental animals there was an individual va-



riation from patient to patient in the susceptibility of the several coagulation factors to fever temperatures. The observations in the human subjects differed further in that the major decrease in the coagulation elements occurred only some time after the defervescence of fever and the compensatory regeneration and recovery became apparent after a considerably longer latent period than was reported in the experimental animals.

A marked decrease in prothrombin followed 10 hours of therapy in the first patient (chart 4). This is the only patient who was not given large

O-3987. C.B. ♂  
Aged 28 years.

FEVER THERAPY—3rd. Treatment.  
Duration of Fever:  $106^{\circ}$ – $107^{\circ}$ =6 hours.  
G.C. Arthritis

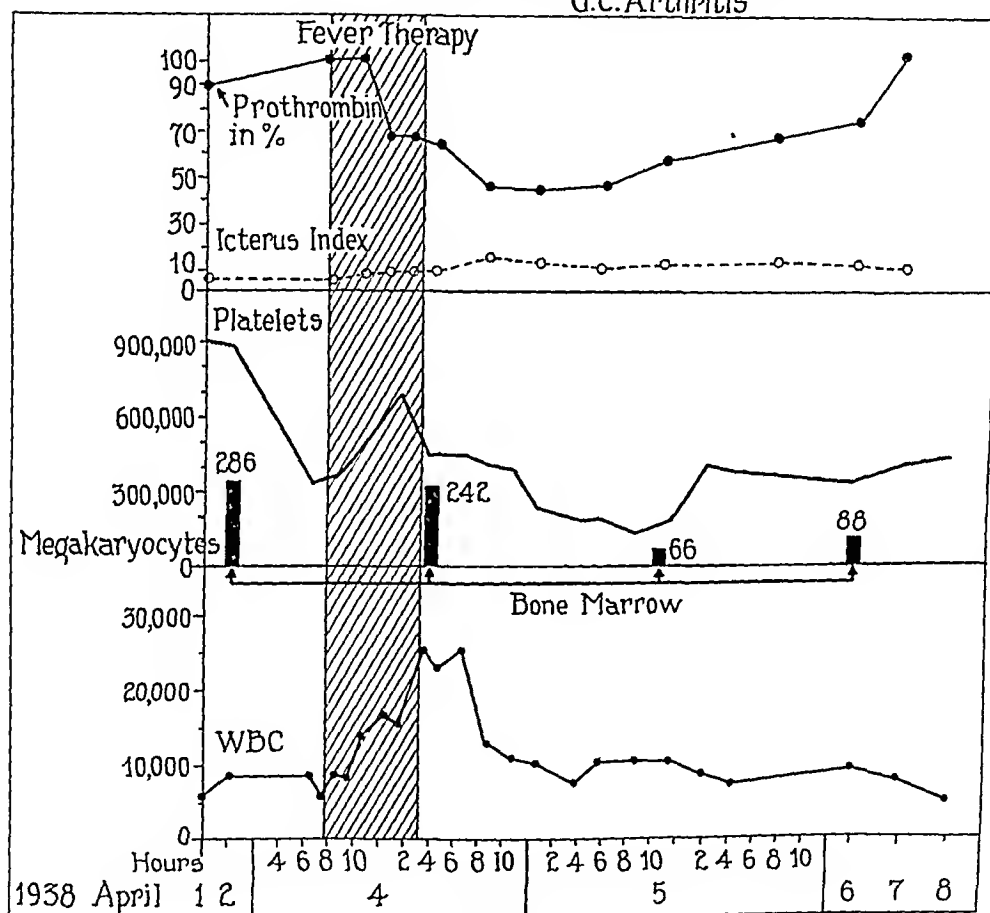


CHART 5.

amounts of glucose preparatory to hyperthermia. During the actual treatment there was a slight elevation in the blood platelets and only a slight decrease in the prothrombin. Immediately after hyperpyrexia there was a retention of bromsulphalein, 15 per cent in one-half hour and 5 per cent in one hour. There had been no retention previous to treatment. The galactose tolerance and hippuric acid tests could not be repeated because of nausea and vomiting. Sternal puncture at this time revealed, in addition to dam-

aged megakaryocytes, an increase in the phagocytic clasmatocytes and a decrease in the more mature neutrophilic myelocytes as contrasted with the pre-fever marrow study. Subsequently there was a progressive decrease in prothrombin and blood platelets and a gradual increase in the icterus index to 70 units, 72 hours post-fever. Hematemesis occurred on the second post-fever day, at which time the prothrombin reached its lowest point of 11 per

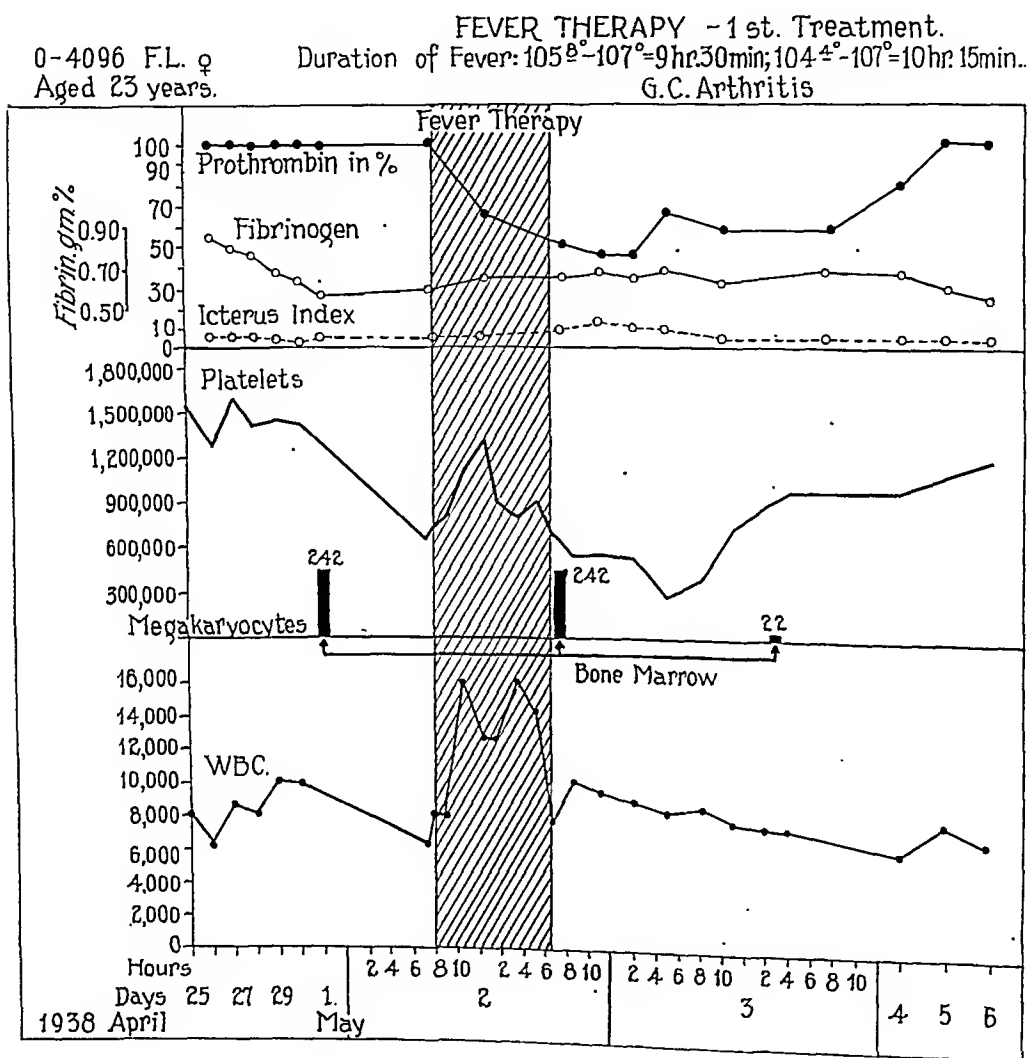


CHART 6.

cent of normal and the platelets were only 200,000 per cu. mm. Both of these coagulation factors had returned to normal by the seventh post-fever day. In the second patient, fortified by glucose during the 48 hours pre-fever, the decrease in prothrombin and in blood platelets did not progress only after the body temperature had returned to normal. Immediately post-fever there was a retention of 20 per cent bromsulphalein in 30 minutes

0-2065 E.M.R. ♀ Post Splenectomy (5yr. 10mo.) for Purpura Hemorrhagica: G.C. PELVIS, Acute.

Aged 21 years.

### Fever Therapy

Duration of Fever:  $106^{\circ}-107^{\circ}=10$  hr.

$104^{\circ}-107^{\circ}=11$  hr. 15 min.

### Fever Therapy

Duration of Fever

$105^{\circ}-106^{\circ}=5$  hr. 15 min.

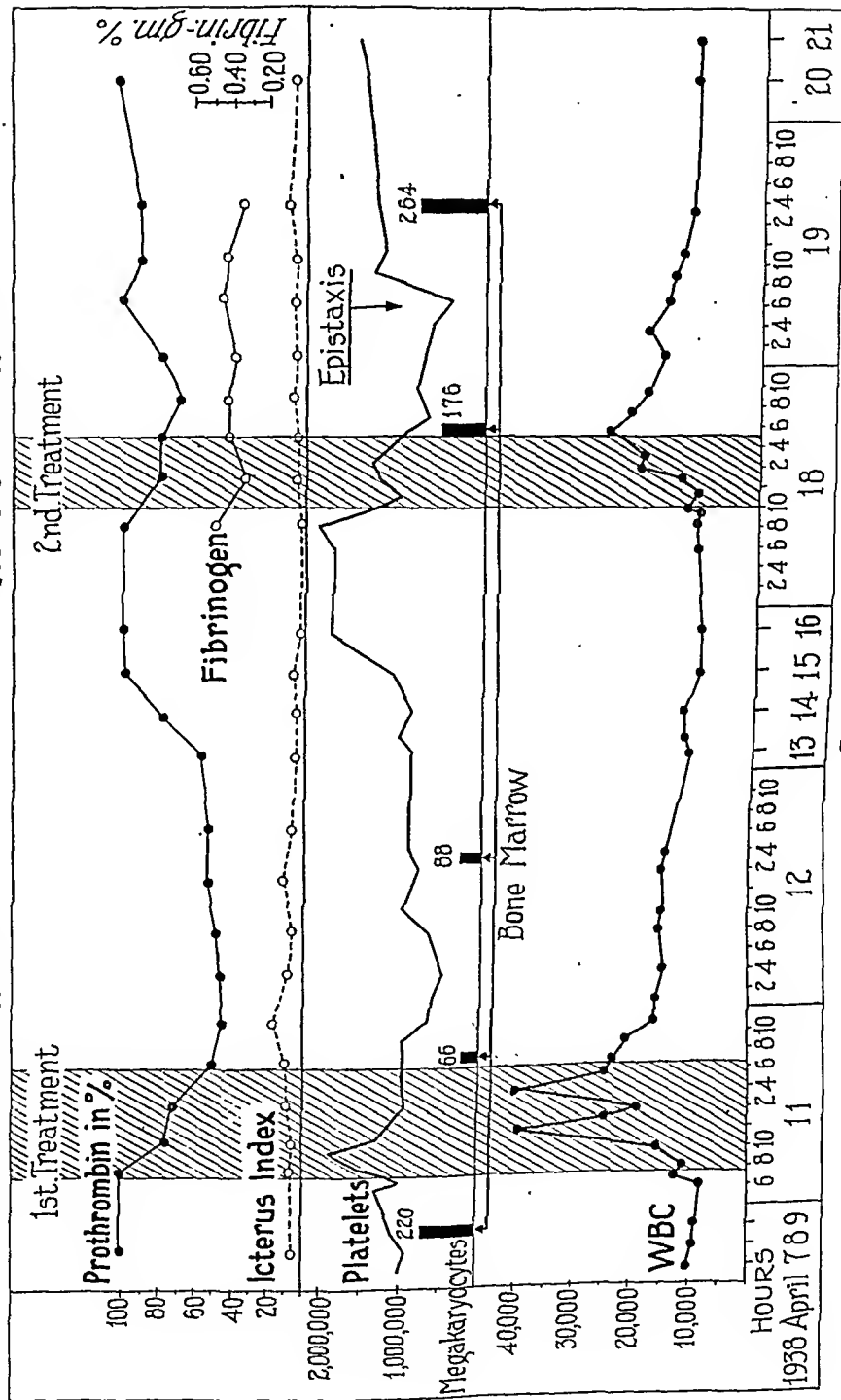


CHART 7.

and 10 per cent in one hour. The highest elevation reached by the icterus index was 13.9 units, five hours post-fever. In addition to damaged megakaryocytes in the bone marrow, there was a moderate "left shift" in the neutrophilic myelocytes and an increase in the highly phagocytic clasmato-cytes. Normal equilibrium had been reestablished by the seventh post-fever day.

Observations on the third patient (chart 6) included the effect of hyperpyrexia on fibrinogen. During the period of control observations previous to the fever treatment, a decrease in the blood platelets and fibrinogen was recorded coincident with the gradual subsidence of the more acute arthritic symptoms in the patient. The therapeutic fever had no further effect on the

### ETIOLOGY OF HEMORRHAGE IN ARTIFICIALLY INDUCED FEVER

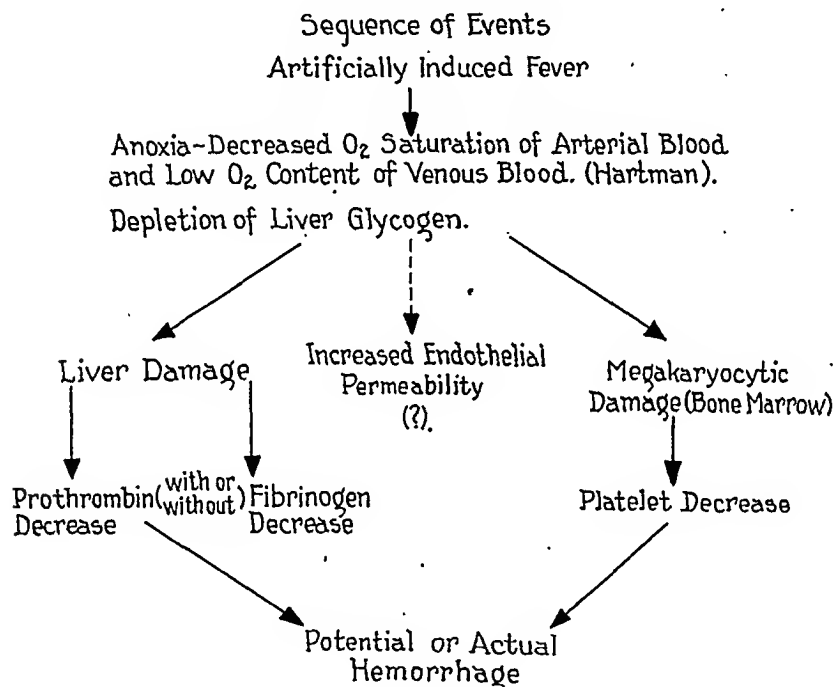


CHART 8.

amount of fibrinogen in the blood plasma. Some deleterious influence on liver and bone marrow, however, was reflected by a moderate decrease in prothrombin and blood platelets as in previous patients, but not to the same degree. A liver function test immediately post-fever showed 15 per cent retention of the bromsulphalein dye in 30 minutes and 10 per cent in one hour. The bone marrow revealed definite nuclear megakaryocytic damage, but no decrease in neutrophilic elements and no increase in phagocytic clasmato-cytes. There was a complete return to normal of all factors by the fifth post-fever day.

An especially interesting study of the effect of hyperpyrexia on the several coagulation factors was made in a former patient from our hematologic

clinic who had had a splenectomy three years and 10 months before for thrombocytopenic purpura (chart 7). No bleeding of any kind had occurred in the interim and two normal pregnancies had been uneventfully consummated. Two fever treatments, the first of 10 hours, the second of five hours duration, were given for an acute gonococcal pelvic inflammatory infection. After each treatment there was a temporary decrease in prothrombin and blood platelets. Epistaxis occurred after the second treatment with moderately depressed prothrombin and with the platelets at their lowest level, 404,520 per cu. mm., the majority being extremely small and qualitatively altered units. There was no recorded change in the fibrinogen. Whereas there had been no retention of bromsulphalein before hyperpyrexia, after the first treatment there was 14 per cent retention in 30 minutes and 12 per cent in one hour, and after the second treatment there was 10 per cent retention in 30 minutes and 8 per cent in one hour. The bone marrow revealed moderate megakaryocytic damage and an increase in the phagocytic clasmatocytes after each treatment. There was a rapid return of all elements to normal after each treatment.

#### DISCUSSION

Hartman<sup>3</sup> has shown that hyperpyrexia may lead to anoxia. It is a well established fact that prolonged anoxia will result in damage to the hepatic cells. Liver damage has been found to accompany the anoxia which occurs during anesthesia.<sup>25</sup> Hepatic cell injury is more readily accomplished with chloroform in an undernourished animal than in the well fed animal whose hepatic cells are full of glycogen. Acute parenchymatous degeneration of the liver cells has been described in all the human subjects examined post mortem following death attributable to therapeutic fever.

Microscopic examination of the liver in the experimental animals in this series revealed acute liver degeneration, the damage being mild in degree in some animals, more marked in others, the quantitative blood prothrombin and fibrinogen determinations being directly proportional to the extent of the tissue destruction.

The state of the liver in human subjects could only be studied indirectly by means of the various tests for liver function. A pathologic retention of bromsulphalein occurred in each instance and was accompanied by a more or less marked increase in the icterus index. A decrease in prothrombin was observed in each patient studied, being more marked in some than in others. The fibrinogen was apparently not affected under the conditions existing in these studies, which finding is in accord with the results reported recently by Ham and Curtis.<sup>26</sup> Prothrombin is thus affected more sensitively than fibrinogen, probably on the basis of the relative degree of liver damage necessary to interfere with these respective functions as described by Smith, Warner and Brinkhous.<sup>16</sup> It is significant that the most marked disturbance in hepatic function occurred in the patient who was not given extra glucose during the immediate prefever period.

Hyperpyrexia under the conditions of these observations, invariably resulted in a decrease in the blood platelets, both in the experimental animals and in the human subjects, recovery taking place more promptly in the former than in the latter. In human subjects the fall in the platelet level occurred in the post-fever period, following a transitory increase during the actual fever episode. Following the thrombocytopenia there was a slow return of the platelets to the circulation. The changing level of the platelets in the peripheral blood reflected directly the state of the megakaryocytes in the bone marrow. There was definite cytoplasmic and nuclear damage during the thrombocytopenic period. The resumption of a normal platelet level was accomplished only after megakaryocytic regeneration was complete in the bone marrow. The decrease in platelets was not mediated through any splenic factor as the same changes occurred in one of our patients who had had a splenectomy for thrombocytopenic purpura approximately four years previous to hyperpyrexia.

The sequence of events in the pathogenesis of hemorrhage in artificially induced fever may then be reconstructed as follows: the rise in temperature causes anoxia and a depletion of the liver glycogen, which in turn result in hepatic damage. With sufficient liver damage (more likely to occur during glycogen deficit) there is a decrease in prothrombin with or without a decrease in fibrinogen. The injury to megakaryocytes is reflected by a decrease in the circulating blood platelets. Damage to the endothelial cells has not been demonstrated morphologically.\* The decrease in platelets, prothrombin and fibrinogen individually and collectively, contribute to potential or actual hemorrhage.

#### CONCLUSIONS

The effect of artificially induced fever on factors important in the coagulation of blood has been studied in experimental animals and in selected human subjects.

A decrease in prothrombin and fibrinogen occurred secondary to liver damage. A decrease in prothrombin may occur without a decrease in fibrinogen.

Artificially induced fever resulted in a relative and absolute thrombocytopenia. The megakaryocytes in the bone marrow showed definite cytoplasmic and nuclear damage. The degree of thrombocytopenia depended upon the extent of the megakaryocytic damage.

The pathogenesis of hemorrhage in artificially induced fever may be followed in orderly sequence: the elevation of body temperature results in anoxia and a depletion of liver glycogen; these factors may result in hepatic and megakaryocytic damage following which there is a decrease in prothrombin and circulating platelets. Fibrinogen may also be decreased. Any

\* Since this manuscript was submitted for publication, Rossman<sup>27</sup> has reported low levels of capillary resistance, measured by a negative pressure suction test, during artificially induced fever.

decrease in these factors important in the coagulation of blood, contributes to potential or actual hemorrhage.

The regeneration of the damaged parenchymatous tissues apparently takes place quite promptly and completely, the changes being reversible within the usual limits of therapeutic application. Any lack of appreciation of the full significance, however, of the facts of mineral, carbohydrate, oxygen, vitamin and water metabolism in fever therapy might lead to irreversible changes and serious permanent damage or death.

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## PARASITOLOGY; A ROUND TABLE DISCUSSION\*

By ERNEST CARROLL FAUST, *New Orleans, Louisiana*

THE subject of Parasitology is entirely too comprehensive to be treated as a whole in this round table discussion, because it may be interpreted as including not only the field of Animal Parasitology, but also that of Bacteriology, of Mycology, of the viral diseases and of spirochetal infections. Since all of the questions which were submitted to me, with one exception, are in the field of Animal Parasitology, and since I am competent to consider only that subject, discussion will be limited to this field.

Even Animal Parasitology is an extremely large subject, in which a tremendous amount of progress has been made during the past decade, particularly on the clinical and epidemiological sides. I realize that a physician—a practicing physician who is busy with his patients—cannot be a master of all phases of Animal Parasitology. However, it is important for him to know (1) the recognizable characters of the organisms which parasitize man; (2) the most efficient methods of diagnosis; (3) the sites where the parasites reside in the human body; (4) whether or not the parasites are always pathogenic or are potentially pathogenic; (5) if pathogenic, what local and systemic changes they produce in the body; (6) what cardinal symptoms they evoke; (7) what therapeutics is most efficient well within the tolerance of the patient, and (8) how to prevent infection or reinfection.

As residents in North America, we are interested primarily in those animal parasites which reside in our own area, and especially those which are either prevalent or are clinically important. I make this distinction because some parasites of man, which are relatively common, are non-pathogenic, while others are of considerable clinical significance. In North America, the following forms fall into one or the other of the two categories mentioned:

(a) *Intestinal Protozoa*. The intestinal forms include the intestinal amebae (of which there are *Endamoeba histolytica*, the pathogenic form, and five non-pathogenic species), and the intestinal flagellates, as *Trichomonas*, *Chilomastix* and *Giardia*.

(b) *Intestinal Helminths*. There are several relatively common species of intestinal helminths, including *Ascaris*, the seatworm or pinworm (*Enterobius vermicularis*), the American hookworm (*Necator americanus*), *Strongyloides*, the whipworm (*Trichocephalus trichiurus*), the beef tapeworm (*Taenia saginata*) and the dwarf tapeworm (*Hymenolepis nana*).

This list is not exhaustive but contains the more prevalent of the intestinal parasites in our area. Of the intestinal Protozoa and most of the roundworms and the dwarf tapeworm, we find a higher incidence in the

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South than in any other parts of the country, while the beef tapeworm is well distributed throughout the continent of North America.

In addition to these intestinal forms, we have the so-called "trichina" worm (*Trichinella spiralis*). This is relatively common as a clinically important parasite in the East, North and West of the Continent, but is rarely of clinical significance in the South.

Aside from these forms, we have one other group of protozoan parasites, the malaria plasmodia, which are of distinct clinical and public health importance in the warmer zones of North America, not only in the Gulf Coast and South Atlantic States, but extending as far north as the Great Lakes and even into the Far West, in the Columbia River Valley and in the Imperial and San Joaquin valleys in California.

I have attempted more or less to unify this Round Table discussion, based on the questions which were presented. The three important topics that have been requested are: (1) amebiasis, and the intestinal flagellate infections; (2) the intestinal helminthiasis, and (3) the rôle of animal parasites in pulmonary disease. We shall take them up *ad seriatim*. After a consideration of each of these topics, the round table will be opened for general discussion.

#### AMEBIASIS

*Etiology and Geographical Distribution.* Amebiasis is the clinical entity which is produced by *Eudamoeba histolytica*, the ameba which invades the tissues of the human body. It is distributed quite generally over the Globe, from the Tropics to the outer limits of the Temperate Zones. It is more common in the Tropics than along the Gulf Coast States. It is more common here in the South than it is in the northern part of the United States, but surveys that have been made in Tennessee, in New York City, Philadelphia, Chicago, Rochester (Minnesota), San Francisco, Los Angeles, Montreal, Saskatoon (Saskatchewan), and in many other localities indicate that this ameba is quite widely distributed throughout the Continent of North America.

*Pathogenicity.* There is essential agreement that *E. histolytica* is either actually pathogenic or is potentially pathogenic. There is no conclusive evidence that it is ever intrinsically non-pathogenic or lacks the potentialities of pathogenicity.

*Types of Amebiasis.* Based on various conditioning factors, we have different pathological and clinical types of amebiasis. Some of these factors are as follows:

(1) *The Levels of the Bowel Which Are Invaded.* In general, *E. histolytica* invades or has the possibilities of invading any site in the large bowel and the last few inches of the ileum, but the two areas in which the preponderance of lesions occurs are the region of the cecum, appendix, and adjacent colon (*cecal amebiasis*), and the rectum and sigmoid (*rectal amebiasis*). Those areas, more than any others in the bowel, are pathologically and

symptomatically significant, and this fact must be taken into consideration in evaluating the problem of amebiasis.

(2) *The Depth of Invasion of the Bowel Wall.* In some instances, there is very shallow invasion, only the superficial portion of the mucosa being invaded and necrosed. In other cases, perhaps in the majority, some of the amebae get down into the submucosa and muscular coats, to form pockets and to spread out by radial extension and coalescence. The lesions in uncomplicated amebiasis are, of course, superficially discrete and distinct from one another. They may be few in number or they may be "peppered" into the mucosa of the large bowel. While they may be confluent below the mucosa, examination of the surface usually will reveal only discrete lesions, in contrast to bacillary infection, in which extensive superficial areas are involved.

(3) *Primary and Secondary Foci.* Both experimental and postmortem evidence favors the view that a majority of the primary sites, where the amebae become attached to the intestinal wall, or obtain a foothold, are in the region of the cecum and the appendix, although in some patients colonization may first occur lower in the bowel. Secondary foci may develop from the extrusion, from the primary lesions, of amebic progeny, which become implanted in other sites lower in the bowel. Likewise, when amebae get down deep enough to invade the mesenteric venules, they are carried to the liver, the organ in which the highest incidence of amebiasis occurs outside the bowel. In the liver, there may be small multiple foci or one or more large abscesses. By extension through the diaphragm, the amebic process may reach the pleural cavity and the lungs. However, there is the possibility that amebae may get out of the bowel wall through the mesenteric lymphatics and become implanted in the lungs, without ever having passed through the liver; or they may pass through the pulmonary capillaries and become implanted in foci beyond the lungs. Thus, there are cases of amebiasis of the brain, spleen, urinary tract, the lymphatics and the skin, and one authentic report each of amebiasis of the epididymis and the scrotum. Most frequently, cutaneous amebiasis is a direct perianal extension from foci just within the rectum.

*Symptomatology.* The next phase of the subject embraces the symptoms that are evoked by the presence of *Endamoeba histolytica* in the body. They are usually classed as acute, subacute, chronic or carrier types. The older classification is based primarily on our previous conception of symptoms, namely, dysentery or profuse diarrhea produced by amebic lesions in the lower portion of the colon and the rectum. However, this conception is quite unsatisfactory, since we now realize that the most common focus of infection is at the level of the cecum, appendix and ascending colon. This cecal type of amebiasis is frequently unaccompanied by dysentery, or the signs or symptoms that are so closely associated with the rectal or sigmoid type. In the cecal type, there may be evidence of a subacute or a chronic appendicitis, or a suggestion of gall bladder disease, or of peptic ulcer; or

there may be only a general malaise. We are now reorganizing our clinical classification of amebiasis, based on the new conceptions. Furthermore, many so-called "carriers" actually have symptoms, provided care is taken in discovering the symptoms. Yet there are many carriers, perhaps the majority, who have no objective or subjective evidence of tissue invasion, although there is always the likelihood that they will develop a clinical amebiasis whenever their threshold of resistance is sufficiently lowered.

*Diagnosis.* Diagnosis may be based on subjective and objective symptoms, on the gross character of the stool; whether, in the dysenteric type, there is an excess of red blood cells or white blood cells, and on the type of tissue exudate. However, only microscopic examination of the stools provides specific evidence of infection. When we examine stools for amebae, we grossly classify them as liquid (i.e. diarrheic, dysenteric, and the like), semi-formed or formed. In the unformed stool, it is not common to find any stage of *E. histolytica* except the trophozoites, the motile stage of the parasite. On the other hand, in the formed stool, we find no trophozoites, only the encysted stage, or occasionally the precyst. The unformed stool should be examined while fresh. By fresh, we mean that it should not be allowed to cool, that it should be examined within half an hour after it is passed. Although, at times, trophozoites survive a longer period, this chance should not be taken. Well-formed stools may be kept 24 hours in a cool place without endangering diagnosis.

In addition to fecal examination, we have examination of proctoscopic material. If amebae are actually found by proctoscopic technic, there is no question about the diagnosis, but a negative proctoscopic examination does not necessarily mean a negative diagnosis, because the major portion of the bowel cannot be examined by the proctoscope. Then, there is roentgen-ray examination, which is more likely to provide suggestive evidence for lesions in the upper half of the large bowel than for the lower half. At times, the roentgen-ray film shows "moth-eaten" or other types of defects which might be due to amebic ulceration, but the roentgen-ray should never be used to take the place of microscopic examination for the diagnosis of amebiasis.

I know of no new or better way of making diagnosis than recovering the organisms by means of microscopic examination of the patients' feces or by examination of material obtained through the proctoscope or following a saline purgation or enema. Let me reemphasize the necessity for having fresh material; if it is liquid, after standing for hours, it is usually undiagnosable, or, at best, it places the diagnostician in an embarrassing position. For trophozoites, we, in our laboratory, as those in many other laboratories, examine coverglass mounts of the direct fecal film, unstained and iodine-stained, by making two side-by-side preparations, one an unstained fecal film made up in one or two drops of physiological salt solution, and the other, after adding and mixing one drop of D'Antoni's iodine stain to the fecal material. For cysts, however, we have now perfected the zinc sulphate cen-

trifugal floatation technic. This technic concentrates cysts many-fold compared with the unconcentrated film, and has the advantage over brine floatation in that the cysts are essentially unshrunk. They are not only in a diagnosable condition but also in a viable state, so that if you wish to plant them for culture growth, they are available for that technic. In some laboratories the hematoxylin-stained preparations are used. They have the disadvantage of requiring several hours to prepare. On the other hand, they have the advantage of providing a more or less permanent film, which can be studied and diagnosed at leisure. Some laboratories prefer them to the iodine-stained film; some prefer the iodine-stained film; some use both.

*The Incidence of Clinical Amebiasis.* Clinical amebiasis is found primarily between 20 and 50 years of age, with the peak between 30 and 40. It is more common in whites than in negroes; more common in males than in females. I do not know about its relationship to the economic status, because most of our private patients who have clinical amebiasis come from the upper economic strata, while most of those in the Clinic come from the lower economic strata. It may be said with certainty that all economic groups of the population are susceptible to infection, but not necessarily equally exposed. There are various predisposing factors to infection, including differences in pathogenicity of the strains of *E. histolytica*, although all North American strains thus far tested have proved to be pathogenic; different predisposing factors within the patient himself at the time he is exposed to infection, as malnutrition (with its invariable lowering of the threshold of resistance), excess of carbohydrates and an insufficiency of proteins, dietary and alcoholic indiscretions, physical and mental strain, worry, loss of sleep, as well as intercurrent infections lowering resistance.

It is impossible to leave this phase of the subject without considering *amebic liver abscess*. This variety of amebiasis was first studied clinically by Sir Leonard Rogers in Calcutta, Musgrave in Manila, Deeks and James in the Canal Zone. The most recent contribution is that of Ochsner and his associates in New Orleans. One of the questions proposed for this discussion was, "How about the correlation of amebiasis with pulmonary tuberculosis?" There is very little information on the subject. In Ludlow's series in Korea (1926) with 150 cases of amebic liver abscess, 10 per cent of those entered the pleural cavity by rupture or extension; only two of the cases had concurrent tuberculosis. In a report of pulmonary amebiasis by Keeton and Hood (1938), tuberculosis was found to be secondary in one of their five cases. These workers indicated, however, that it was frequently difficult to make a clinical diagnosis which would rule out tuberculosis on the one hand and pleural amebiasis on the other, without careful laboratory examinations.

*Treatment.* With reference to the treatment of amebiasis, I shall enumerate the more important drugs, taking them up from the historical point of view. They are as follows:

1. *Ipecac*. This drug was first used in 1829 and popularized many years later by Sir Leonard Rogers in Calcutta, towards the beginning of the present century. Dover's powders and alcestra tablets were later introduced. Although ipecac has been a standard prescription for amebiasis until recently, any physician planning to prescribe this drug should first take a full course of ipecac himself.
2. *Emetin hydrochloride*. This was first proved valuable by Vedder in 1912, and still has its place, but it should not be abused. It is very valuable in reducing acute manifestations but is probably not curative. It should not be prescribed in excess of one grain daily for a total of 12 grains. When given in larger amounts, it has serious sequelae, including degenerative myocarditis.
3. *Bismuth subnitrate*. Deeks, in 1908, introduced this drug in the Ancon Hospital, in the Canal Zone. I know of no specific amebicidal property in this drug. However, it may alleviate the more acute symptoms of amebic dysentery until the patient can obtain specific treatment. It has the special disadvantage of masking the amebae so that they cannot be readily diagnosed microscopically.
4. *Stovarsol* (190 Forneau). This French preparation had its place in its day and still has its advocates. While it constitutes rather a heroic treatment, it has cured many persons who have been able to take a full course of treatment.
5. *Chiniofon* (yatren, anayodin). This drug was first introduced by Mühlens in 1921, and has come to be used as probably the most common drug for the treatment of all types of amebiasis. It has a very high amebicidal rating and a very low toxicity.
6. *Vioform*. Second to chiniofon, in the same chemical series, but containing more iodine, is vioform, which was introduced by workers in California (David, Johnstone, Reed and Leake, 1933). Both chiniofon and vioform are usually prescribed in the amount of three or four 4-grain tablets, three times daily, for a period of eight to ten days.
7. *Diodoquin*. This drug is relatively inefficient, because it is not readily absorbed by the bowel wall, and hence does not reach the organisms in the deeper layers of the bowel.
8. *Carbarson*. About the same time that vioform was introduced clinically, carbarson was introduced by Anderson and Reed (1931) in California. The dose prescribed is usually two 4-grain tablets daily for eight to ten days.

In passing, I wish to state that at times one of the usual amebicidal drugs may not completely eliminate the infection. In that case, one of the other available drugs should be utilized.

## INTESTINAL FLAGELLATE INFECTIONS

In referring to the intestinal flagellates, mention may be made, in passing, of *Trichomonas* and *Chilomastix*, which live in the lumen of the cecum and, in so far as we know, are not tissue invaders. *Giardia* lives primarily in the region of the duodenum. It also is not a tissue invader; however, it has a ventral adhesive disc, by which it can attach itself to the cuticula of the mucosa, so that, in tremendous swarms, as exist in many *Giardia*-infected patients, it is possible for *Giardia* to produce a superficial erosion of the mucosa, with an excess of mucus, and a mucous diarrhea. Since 1937 atabrine, administered as in malaria, has been utilized in the treatment of 417 cases of giardiasis, with eminently successful results. Chiniofon is at times helpful; carbarsone may be helpful. At times neither of these drugs produces more than a temporary diminution in the mucous diarrhea or in the number of organisms in the bowel. Glauber salts may be given as a temporary palliative.

Before I pass on, are there any questions on amebiasis or flagellate infections of the intestinal tract?

Question: What percentage of zinc sulphate is used in the zinc sulphate centrifugal floatation technic?

Answer: It is made up as a 33 per cent aqueous solution of zinc sulphate U.S.P., having the specific gravity 1.180.

Question: What about the technic for diagnosis of amebae in the tissues at post-mortem?

Answer: If a "fresh" autopsy has been secured, routine hematoxylin-eosin preparations are satisfactory. For older sections, the addition of Best's carmine to the hematoxylin-eosin technic stains the amebae a strawberry red, so that they can be readily found and identified.

Question: Do you consider carbarsone valuable?

Answer: Yes, but hardly as satisfactory as chiniofon and somewhat more toxic.

Question: Has diodoquin been proved to be satisfactory for amebiasis?

Answer: Cases treated with this drug are more likely to relapse, because the drug is not readily absorbed by the deeper layers of the bowel and thus kills only those amebae near the surface.

Question: What is your opinion about serologic tests for amebiasis?

Answer: Complement-fixation has proved to be at least 90 per cent specific in diagnosis. I think it is particularly valuable as a post-treatment check in patients whose feces are repeatedly negative.

Question: Is there any correlated blood change in amebiasis?

Answer: In uncomplicated amebiasis there is no blood change.

Question: Do you use the iodine in the tincture form for staining amebae?

Answer: We use D'Antoni's iodine solution. The stock is made up as a saturated solution of iodine in a 1 per cent aqueous solution of potassium iodide.

Question: Have you used quinine for the treatment of giardiasis?

Answer: I have had no experience myself.

Question: It was used in one case in Philadelphia.

## INTESTINAL HELMINTHIASES

The next phase of the subject deals with intestinal helminthiases. I shall confine consideration exclusively to treatment. I might mention, however, that ascariasis and dwarf tapeworm infection are found more frequently in younger children, while the other helminthic infections are more prevalent in older children and adults. Diagnosis is made by recovery of worms or their segments, their eggs or larvae.

We have some anthelmintics which have been handed down to us from the ancients, as infusion of the bark of *Punica granatum*, *semen contra*, and decoction of male fern; others from American aborigenes, as oil of chenopodium and leche de higuerón. From the Greeks came the unrefined plant products from which we have obtained thymol, santonin, oil of chenopodium (with its effective fraction, *ascaridol*), the oleoresin of male fern, and from the Egyptians, pomegranate bark from which we have extracted pelletierin tannate or pelletierin hydrochloride. Those drugs which were pharmaceutically and biologically tested before they were used clinically include carbon tetrachloride, tetrachlorethylene, hexylresorcinol and gentian violet. From these groups, I shall mention certain drugs which are particularly recommended for their combined efficiency and safety.

1. *Ascariasis*. The drug of choice is hexylresorcinol, in the form of caprokol pills, with hard gelatin coating, on the market in 0.2 gm. size and soon available also in 0.1 gm. size for small children. The dose for adults is 1 gm., taken in the morning on an empty stomach, and followed by a four to five hour fast. In ascariasis, I advise post-treatment saline purgation to secure rapid evacuation of dying worms, which might otherwise produce acute intoxication of the patient, due to absorption of their products of decomposition.

2. *Oxyuriasis*, or pinworm infection. Prescription of caprokol pills, as indicated above in ascariasis, followed the same night by retention enemas of hexylresorcinol 1:1000 solution (S. T. 37 undiluted) after the large bowel has been cleaned out with high tepid water enemas, has proved fairly effective. As an alternative, gentian violet therapy, given in the form of seal-ins-coated tablets (one grain three times daily for a period of a week or eight days, then rest a week, then a second period of a week or eight days' treatment) may be employed, and has been found to have a 90 per cent efficiency. However, pinworms in a family or institutional groups will not be eliminated unless all infected members of the group are treated until they are cured.

3. *Hookworm infection*. Both tetrachlorethylene and carbon tetrachloride are very efficient. Tetrachlorethylene is preferable because it is almost insoluble in water and, therefore, in the absence of alcohol or absorbable oils, is essentially non-toxic, since it is not absorbed by the bowel wall. In utilizing either drug, both pre-treatment and post-treatment purgation with Glauber salts is recommended, not only to clean out the bowel but



to remove the mucus from around the heads of the worms, thus allowing the drug to act more rapidly through the mouth of the worm.

4. *Trichocephaliasis* or whipworm infection. There is no safe, specific drug available in the United States. In Tropical America, the leche de higuerón, or juice of *Ficus glabrata*, either fresh or preserved in 1 to 2 per cent sodium benzoate, is administered in two-ounce amounts. As "Higueronia," it may be obtained from Mexico City or Cali, Colombia, but it is not available in the United States as far as I know. This crude drug, containing the proteolytic enzyme *ficin*, is both very efficient and non-toxic. Oil of chenopodium is efficient, but is so highly toxic in effective therapeutic doses that I hesitate to recommend it. The toxic sequelae may not appear for three or four weeks after administration of this drug. If it is prescribed, the patient must be hospitalized and watched very carefully throughout treatment. It should be preceded and followed by saline purgation.

5. *Strongyloidiasis*. Gentian violet is the only drug that has proved effective in this disease. Enteric-coated tablets of gentian violet medicinal, administered in doses of one grain three times daily before meals for a period of approximately 16 days (or until 50 grains have been administered) are recommended. One or two courses of treatment produce cure in the average cases. For refractory patients, we in the Department of Tropical Medicine at Tulane University, and others following our recommendations, have been giving 25 c.c. of a 1 per cent solution of gentian violet by duodenal intubation, and have had very satisfactory results.

6. *Tapeworm infections*. For tapeworms, whether large or small forms, the oleoresin of aspidium is probably the most satisfactory anthelmintic, but the coöperation of the patient and adequate preparation of the patient are important requisites for successful treatment. Carbon tetrachloride is also quite satisfactory. In prescribing either drug, the patient should be hospitalized or under the direct supervision of the physician. Saline purgation the night before treatment is recommended. The drug is given on an empty stomach in the morning. Carbon tetrachloride is given as a single dose of 3 c.c.; the oleoresin of aspidium in three divided doses of 20 minims each, one-half hour apart. Two hours after the administration of either anthelmintic, there should be post-treatment saline purgation, and no food should be permitted until adequate bowel movements have been obtained. There is one additional suggestion. Some physicians prefer intubation of the oleoresin with magnesium sulphate and mucilage of acacia (oleoresin of aspidium, 60-120 minims;  $\text{MgSO}_4$ , sat. sol., 30 c.c., mucilage of acacia, 30 c.c.). The drug can be intubated under a fluoroscope in the physician's office and requires no post-treatment purgation.

Before passing on to the third section of the discussion, opportunity is offered for questions.

Question: What has been your experience with pumpkin seeds in the treatment of tapeworms?

Answer: My experience with macerated, shelled pumpkin seeds (either taken en

masse, or after a strained decoction has been administered) has been consistently unsuccessful in the removal of the heads of the worm. In this respect, it parallels the meat of the cocoanut, in evacuating a long portion of the worm but in failure to dislodge the head.

Question: Is caprokol or gentian violet treatment of seatworm infection (oxyuriasis) effective in removing the worms?

Answer: Oxyuriasis is usually a familial or an institutional infection, in which the majority of the group harbor the worms. Treatment of one or two members of the group is useless when the other infected members remain untreated. Hence treatment of all infected members of the group, as determined by repeated cellophane swab examinations, is indicated. Several courses of caprokol by mouth, accompanied by hexylresorcinol solution retention enemas, are frequently necessary to remove all of the seatworms in an infected patient. Gentian violet therapy in this infection is promising and deserves thorough clinical trial.

Question: Is there any specific treatment for trichinosis?

Answer: Chemotherapeutics have all been disappointing and convalescent serum has not been particularly helpful. I know of no treatment for trichinosis except supportive management of the patient and palliative procedures.

### THE RÔLE OF ANIMAL PARASITES IN PULMONARY DISEASE

Animal parasites may act either directly or indirectly in the production of disease of the respiratory tracts.

1. *As Causative Agents.* *Ascaris*, hookworm and *Strongyloides* larvae in migration through the lungs may cause atypical pneumonia and *Strongyloides* may become established in the bronchial epithelium. Moreover, these organisms may reactivate pulmonary tuberculosis (Bülow, 1929). Amebiasis of the lungs or pleural cavity must be differentiated from pulmonary tuberculosis, pyogenic abscesses of lungs or bronchopneumonia; also from bronchiectasis (Keeton and Hood, 1938). Pulmonary implantation of hydatid cyst is only secondary in incidence to hepatic hydatid. In Japan, Korea, Formosa, certain districts in China and elsewhere in the Orient, semi-encapsulated adults of the pulmonary distome (*Paragonimus westermani*) typically develop in peribronchial sites, with openings into the bronchioles, discharging necrotic tissue debris, blood and eggs of the worm, with an hemoptysis which requires differentiation from that of pulmonary tuberculosis. In the Orient, Africa and Tropical America, adult blood flukes or schistosomes at times become lodged in the pulmonary arterioles, with multiple abscesses or tubercles around their eggs which are infiltrated in the pulmonary parenchyma.

2. *As Indirect Agents.* Freiman (1927) states: "Malaria forms a good soil for the implantation of tuberculosis and . . . the simultaneous presence of both diseases in the same subject increases the gravity of the prognosis." Collari (1932) observes: If tuberculosis gets a foothold in a chronic malaria patient, it tends to be miliary in type. Induced malaria in a tuberculous patient is invariably contraindicated. Boggian (1934) has found that the supervention of malaria in a tuberculous patient lights up and extends latent lesions. Visceral leishmaniasis or kala-azar produces an absolute lympho-

cytosis with a leukopenia. Hence, in this disease, due to greatly lowered resistance of the patient, bronchopneumonia is a common complication.

Are there any questions on the topic of animal parasites in pulmonary disease?

Question: What treatment do you recommend for hookworm, *Strongyloides* and *Ascaris* larvae in the lungs?

Answer: There is no known safe anthelmintic procedure which will kill hookworm or *Ascaris* larvae in the pulmonary vessels or respiratory tree. Specific treatment must be reserved until the worms have arrived in the intestinal tract. *Strongyloides* larvae, like *Strongyloides* adults that have become established in the bronchial epithelium, are killed by gentian violet administered by vein as a filtered one-half per cent solution, given every third day in amounts not in excess of 25 c.c. at each administration. For this treatment the patient must be hospitalized and under the direct supervision of the physician.

Question: How can one distinguish pulmonary distomiasis from tuberculosis of the lungs?

Answer: In pulmonary distomiasis there is typically a rusty-brown tinge to the blood-flecked sputum. Microscopic examination of the discharge reveals the characteristic golden-brown eggs of the parasite, which give the iron-rust appearance to the sputum.

# CASE REPORTS

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## GRANULOCYTOPENIA FROM SULFANILAMIDE WITH UNUSUAL BLOOD CRISIS AND RECOVERY; CASE REPORT\*

By J. SHIRLEY SWEENEY, M.D., Sc.D., F.A.C.P., and L. E. ALLDAY, M.D.,  
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IN an issue of the *Journal of the American Medical Association* there appeared experimental studies, case reports and an editorial concerning sulfanilamide. Two of these papers<sup>1,2</sup> dealt with the leukocytic response to sulfanilamide and its mode of action. In an interesting and cogent extension of the subject were two case reports<sup>3,4</sup> of fatal intoxication following administration of the drug. Reference was made to two other reports of fatal cases. The subject was reviewed editorially, and one is reminded that the Council on Pharmacy and Chemistry originally advised periodical microscopic examinations of blood of patients taking sulfanilamide.

As with any new therapeutic agent, sulfanilamide has been more or less indiscriminately employed in the treatment of almost every type of infection. In the wake of such uncontrolled exploitation there invariably appear reports of mortality and morbidity. Such was true of dinitrophenol, benzedrine sulphate and other drugs.

That sulfanilamide can cripple the hematopoietic mechanism is undeniable. It would seem, however, that the drug is dangerous only to those individuals who may be sensitive to it. It may be compared in this respect to amidopyrine. Its danger, however, is greater because of its more extensive application.

There are, no doubt, many physicians who have observed unusual or pathological blood pictures in patients receiving sulfanilamide. Anemias, principally of the hemolytic type, leukopenic states of varying degrees, as well as peculiar distributions of the granulocytes, all have been reported. Apparently there is no constant hematopoietic response to this drug. This fact further emphasizes the necessity of watching closely the blood reaction of any patient taking such medication.

The case I wish to report presents two interesting features aside from the polymorphonuclear leukopenia and the anemia. One is the apparent life saving effect of daily transfusions, and the other is the very unusual crisis, not unlike the crisis of pneumonia, which occurred during the treatment.

### CASE REPORT

The patient, a white female, aged 41, was first ill with a sore throat, not unlike others that were prevalent during the winter season in this vicinity. Having had a pharyngitis a few months before, which was relatively mild and for which she was given sulfanilamide by her physician, she began taking the drug again without her

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doctor's prescription. The infection began as a sore throat with a slight elevation of temperature and headache. During the first three days she took 5 grains of sulfanilamide every four hours. On the evening of the third day the temperature was recorded as 104.2° F. At this time she was seen by her physician who prescribed 10 grains of sulfanilamide every three hours for two days. Also, on the evening of the third day and morning of the fourth, the patient became conscious of a sore mouth and slight bleeding from her gums. The temperature continued to rise and on the fifth and sixth days reached 106° F. On the sixth, seventh and eighth days she received 90 grains more of sulfanilamide, making a total of 300 grains. Because of the continued high temperature and bleeding gums, which showed several areas of gangrenous ulceration as also did the hard and soft palates, the patient was admitted to the Medical Arts Hospital.

When first seen in the hospital, there was noticed marked blueness of the lips and nails. The patient was obviously quite ill. She complained chiefly of her mouth, marked dizziness and faintness. Examination revealed marked congestion of the gums with small hemorrhagic areas. There were two large gangrenous areas noted on the upper gum. There were several smaller ulcerations on the roof of the mouth and two or three similar areas on the left tonsil. The pharynx was moderately congested. There was one small gland under the left jaw, and two or three small ones in the right anterior cervical region. The patient, although not truly stuporous, was extremely non-communicative and apparently a victim of considerable prostration. Her temperature on admission to hospital was 104° F., pulse 130, and respiration 22. Her blood pressure was 135 systolic and 90 diastolic. There were no other notable physical findings.

The blood count on admission to the hospital showed 2,680,000 red blood cells and 42 per cent hemoglobin. There were 1,800 leukocytes, of which 4 per cent were polymorphonuclear cells, 1 per cent mononuclear leukocytes, and 95 per cent lymphocytes. The patient was given an immediate transfusion of 300 c.c. of whole blood. On the following day her blood count revealed 3,040,000 red cells, 45 per cent hemoglobin, and 4,150 leukocytes of which 1 per cent were polymorphonuclear cells and 99 per cent were lymphocytes. The patient was transfused daily, averaging 300 c.c. of whole blood with each transfusion. Her condition continued as previously described, temperature ranging from 101° F. to 104° F., and pulse ranging from 120 to 130. The lesions in her mouth and throat remained unchanged during the first several days of her hospitalization. Her responsiveness was likewise unaltered, inasmuch as she remained very quiet and listless. On the sixth day her red cell count was 3,510,000. There were 3,250 white cells, 9 per cent of which were polymorphonuclear cells, and 6 per cent of which were young forms. On the seventh day the white count remained approximately the same, except that 13 per cent of the white cells were of juvenile type. On the eighth day there was a remarkable crisis. This crisis was characterized by a critical drop in her temperature to a subnormal level. Simultaneously, that is within a few hours, a blood count revealed a red cell count of 3,750,000, and 10,400 white cells, 25 per cent of which were polymorphonuclear cells, 6 per cent of the polymorphonuclear cells being young forms. From this point on, the patient showed consistent improvement, the white cells rising on the tenth day to a peak of 19,350, 54 per cent of which were polymorphonuclear cells. Following this, her count dropped to 10,000 odd white cells and on down to 8,300, at which level she fluctuated with a perfectly normal differential picture. Her temperature rose from a subnormal level to a normal one and remained there during the rest of her residence in the hospital. No other therapy was employed except daily blood transfusions.

As intimated in the first part of this case report, the progress of this patient is reported because of the unusual crisis that she experienced, associated with a simultaneous rise in her white cell count; and because of the apparent effectiveness of daily

transfusions. The crisis described was quite similar to the crisis observed in pneumonia, and one that I have never before observed in a blood dyscrasia.

### COMMENT

A case of sulfanilamide intoxication has been reported which shows an unusual leukopenia of a polymorphonuclear type. The picture as first seen had many characteristics of a typical Schultz agranulocytic angina. Because of the history of sulfanilamide medication, a tentative diagnosis of sulfanilamide intoxication was made and daily transfusions were given. There were noted, after about seven days, a critical drop in temperature and simultaneous rise in the polymorphonuclear leukocytes. The purpose of this report is to emphasize the apparent value of daily blood transfusions in suspected sulfanilamide intoxication, and the necessity of periodic microscopic blood examinations.

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## EXFOLIATIVE DERMATITIS DUE TO PHENOBARBITAL WITH FATAL OUTCOME; REPORT OF TWO CASES\*

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PHENOBARBITAL, chemically a white colorless substance, phenylethylbarbituric acid or phenylethylmalonylurea was first placed in the hands of clinicians in 1911 under the proprietary name of Luminal. Introduced as a sedative and hypnotic, its greatest success was in the treatment of epilepsy; and, at the present time, it is probably the most frequently prescribed sedative in modern medical practice.

A few months after its introduction, Loewe<sup>1</sup> (1912) reported the first case of cutaneous reaction due to the ingestion of phenobarbital. He published his observations of three cases, each patient exhibiting a generalized macular eruption, without systemic reaction, the rash fading upon withdrawal of the drug. The literature reveals few additional reports until Heuber<sup>2</sup> (1919) reported the development of a hemorrhagic type of cutaneous eruption allegedly due to phenobarbital medication. Weber<sup>3</sup> (1925) described a case presenting large bullae associated with jaundice, and Hamilton et al.<sup>4</sup> (1926) reported the first case of a universal exfoliative dermatitis due to phenobarbital. In this case the

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patient recovered after a protracted illness, with complete exfoliation including the nails, hair and mucous membranes.

Following the excellent summary of the symptomatology of phenobarbital poisoning by Menninger<sup>5</sup> (1928), in which he collected from the literature only 41 cases of cutaneous eruption due to phenobarbital therapy, a large increase in the number of case reports was noted. Numerous articles were published with every possible type of eruption and all of the cases terminated in complete recovery. Chavany and Vannier<sup>6</sup> (1929) reported the first fatality. They reported two deaths. Their first case was a 30 year old white female who had taken phenobarbital 0.1 gram for nine days before the appearance of the eruption. The patient developed a generalized exfoliative dermatitis with high temperature, increased pulse rate, marked oliguria, and a severe toxemia resulting in death the sixth day of her illness. Autopsy findings showed only a severe congestion of the parenchymatous organs. The second case followed shortly after the preceding fatality. This was a 48 year old white female who had been taking phenobarbital for six months. The dosage had been increased up to 0.6 gram daily prior to entering the hospital. A generalized exfoliative dermatitis developed including the mucous membranes, and the clinical course followed the first case very closely. Death occurred seven days after hospitalization and eleven days after the onset of the eruption. Autopsy findings were not greatly different nor more enlightening than in the first case.

Brunsting<sup>7</sup> (1932) reported seeing a patient on the fifth day of her eruption with a history of having taken a phenobarbital preparation in the amount of one-quarter grain three times daily for ten days. The eruption resembled an acute erythema multiforme, and the clinical course simulated a fulminating pemphigus. Death occurred on the fifteenth day and evidence that phenobarbital was the sole precipitating factor was declared to be only circumstantial.

Millard<sup>8</sup> (1933) reported several cases of dermatitis due to phenobarbital, one terminating fatally. This patient was a 61 year old white male who was given Theominal (phenobarbital one-half grain) three times daily for 18 days. The resulting dermatitis was of a universal exfoliative type, resembling an arsenical dermatitis, and involving the mucous membranes. Autopsy findings showed a bronchopneumonia and chronic nephritis; no arsenic was found post mortem.

Heckmann<sup>9</sup> (1935) reported a fatal case in a five and one-half year old white child being treated with Luminal for an epilepsy of one year's duration. The medication was given in 0.05 gram doses twice daily for from 15 to 17 days before mouth and cutaneous lesions made their appearance. The clinical course was marked by a rather high temperature, evidence of a severe toxemia, and the formation of large bullae with generalized exfoliation including the hair. The patient died on the fourth day of hospitalization; autopsy findings were not significant.

A fatal case was recorded by Scarlett and Macnab<sup>10</sup> (1935) in which the patient, a 17 year old female, was hospitalized because of an acute encephalitis. She was given phenobarbital 1.5 grains at bedtime after hospitalization of one week and at a time when the acute process was apparently resolving. After 12 days on this medication, the patient developed a fever followed by a red macular eruption which rapidly became worse, and which was accompanied by a necrosing stomatitis and rhinitis. Death occurred six days after the onset of

the eruption and autopsy revealed, in addition to the dermatitis, a cloudy swelling of the kidneys and liver, and numerous small and one large hemorrhage in the brain and its covering, indicative of a hemorrhagic encephalitis.

Sweitzer and Laymon<sup>11</sup> (1937) reported four cases of cutaneous reaction due to barbituric acid derivatives, of which three terminated fatally. Their first case, a 48 year old white female, was given one and one-half grains of phenobarbital for approximately three weeks, at which time a red itchy eruption made its appearance. The eruption, at the time of hospitalization two weeks later, was universal except for the palms and soles, red, scaling and accompanied by an increased temperature, pulse and respiration. The patient died after 12 days of hospitalization and autopsy findings showed the presence of gall stones, fatty changes in the liver and terminal bronchopneumonia in addition to the exfoliative dermatitis.

Their second case was 58 years of age, and was hospitalized because of coronary sclerosis, auricular fibrillation and a possible lung infarct. Butyl-ethyl barbituric acid (three grains) daily was given the patient for approximately 50 days. Vesicular lesions later becoming almost hemorrhagic, together with a red and swollen throat, comprised the dermatologic picture, accompanied by an agranulocytosis of marked degree. An autopsy was refused.

The third fatality was a white female 67 years of age who had been given sodium pentobarbital for ten days. A red pruritic cutaneous eruption appeared the fourth day after medication was initiated, and, due to discomfort, the medication was continued prior to hospitalization. The patient died after five days in the hospital, having developed an anuria, edema of the extremities and a terminal pulmonary edema. An autopsy was not obtained.

Because of the comparative rarity of such cases, and with the view also in mind of bringing to the attention of the medical profession the possible dangers of phenobarbital medication, a summary of two fatal cases observed at the University Hospital is presented.

#### CASE REPORTS

*Case 1.* C. R., a white male, aged 48, dentist, was admitted to the University Hospital, February 20, 1934, with a chief complaint of general weakness and difficulty in breathing. The patient had noticed a moderate generalized weakness for three or four months with labored breathing on exertion, and an increase in the symptoms the two weeks prior to entering the hospital. He had also noticed a nervousness which he ascribed to financial and business difficulties. His past history was not suggestive of serious illness.

Physical examination showed the patient to be a well developed and well nourished middle-aged white male with a rather apprehensive appearance. The breathing was somewhat labored but not increased in rate. There was no clubbing of the fingers. The skin was of normal color and texture. The eyes reacted normally; the nose and throat appeared normal. The oral cavity showed some carious lower teeth, the upper jaw being edentulous. The thyroid was normal. The thorax was symmetrical and without external abnormalities. The heart was not enlarged to percussion, the rate and rhythm normal with no murmurs heard. Blood pressure was 125 mm. systolic and 70 mm. diastolic. The lung fields were clear to percussion and auscultation with equal and ample excursion. The abdomen presented no masses or tender areas; the spleen and liver were not enlarged. The extremities presented no change except a slight tremor of the fingers. Rectal examination showed a few external hemorrhoids; the genitalia were normal. The deep and superficial reflexes were physiologically normal.



The patient was seen by the Department of Neurology, who found no organic disease present. The Department of Neuropsychiatry made a diagnosis of a psychoneurosis with fatigue reaction in a compulsive type of individual.

The laboratory findings were as follows: urine examination was normal. The blood count showed: hemoglobin 89 per cent (Sahli); red blood cells 4,500,000; white blood cells 10,150; differential count: polymorphonuclear leukocytes 72 per cent; lymphocytes 23 per cent; monocytes 4 per cent; basophiles 1 per cent. Stool examination for blood and parasites was negative. A specimen of sputum showed no acid-fast bacilli, but spirochetes were found to average two per high power field. Frontal stereoscopic examination of the thorax was done February 21, 1934, with the following reading: moderate peritruncal infiltration, somewhat generalized, more prominent in the region of the right lower stem bronchus. An electrocardiogram taken February 23, 1934 was normal.

Medication was symptomatic and was given in the form of luminal one-half grain three times a day and one and one-half grains at bed-time. He was also given 0.25 c.c. adrenalin solution without effect on his moderately dyspneic breathing. He was discharged March 2, 1934, with a prescription for luminal to be taken if necessary for rest. The total amount of luminal taken in the Hospital was 28.5 grains.

The patient was readmitted March 15, 1934, in a semi-comatose condition. The history revealed that immediately after discharge, March 2, 1934, he developed a fever with the appearance of red "blotches" about the face which gradually spread to the trunk and extremities. Accompanying the cutaneous eruption the patient developed a sore mouth and throat, so severe that no food or liquid had been taken for a period of four days. The wife stated that one luminal tablet (0.032 gm.) was given three times daily since leaving the hospital and continued until four days before admittance. (Total of 13.5 grains luminal taken at home.)

Physical examination on admission March 15, 1934, revealed the patient to be acutely ill with a rectal temperature of 103° F., pulse of 100, and with a generalized cutaneous eruption consisting of erythematous maculo-papular patches showing a tendency to confluence. This was especially true about the face and arms, where marked exfoliation was seen (figures 1 and 2). Pitting edema was present not only in the lower extremities but also about the trunk and upper extremities. The mucous membranes showed large vesicles, for the most part ruptured, leaving denuded surfaces covered with a whitish muco-fibrinous material. The lips were swollen, edematous and fissured; swallowing was accomplished with great difficulty.

The patient was placed on a regime of saline purgations, colloidal baths, intravenous sodium thiosulphate and large amounts of intravenous glucose and sodium chloride solutions. He continued to run a septic type of fever ranging between 101° F. and 105° F., pulse rate from 90 to 130 per minute and respirations from 15 to 30. The semi-comatose state present on admission continued until March 19, 1934, at which time considerable clearing of the mental faculties was noted. There were no abnormal physical findings except the cutaneous eruption and the fever.

A roentgen-ray film of the chest taken March 16, 1934, showed a peritruncal infiltration of both bases, predominantly right, and definite increase in density over the previous films taken February 21, 1934. The urinary output, at first suppressed, rose to normal amount with no abnormal findings on repeated examination. The blood picture was within normal limits except during the last two days when the following blood picture was found: hemoglobin 75 per cent (Sahli); red blood cells 4,150,000; white blood cells 24,000; polymorphonuclear leukocytes 94 per cent; basophiles 2 per cent; lymphocytes 1 per cent; monocytes 2 per cent; myelocytes 1 per cent. A blood culture was negative. Stool examinations were negative. Repeated sputum examinations revealed no acid-fast organisms or spirochetes, but did show numerous encapsulated lanceolate diplococci.

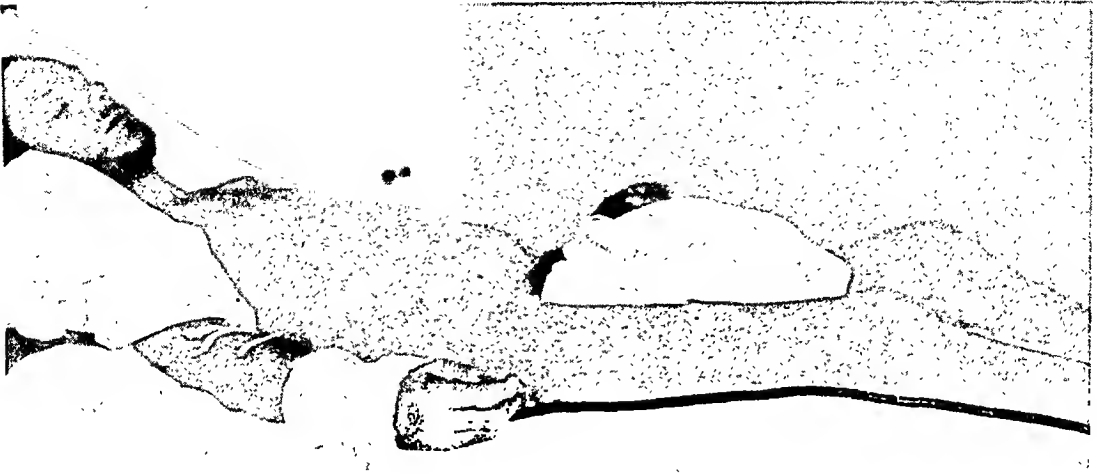


FIG. 1. Case 1, C. R., appearance of eruption at time of admission, February 20, of a maculo-papular type and tending to become confluent.

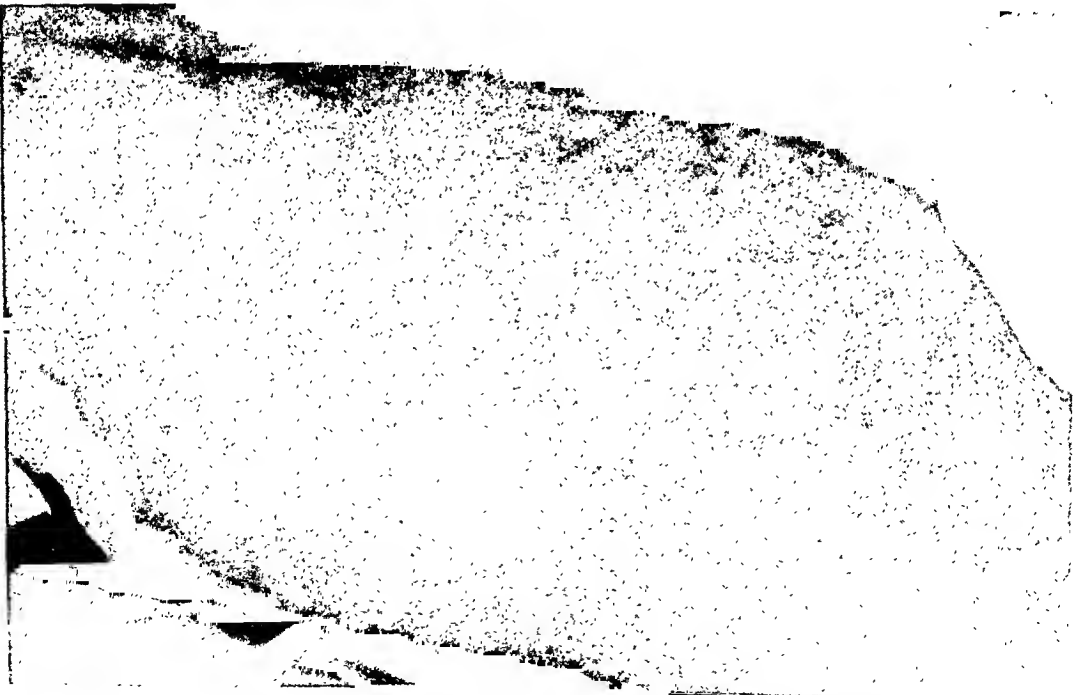


FIG. 2. Case 1, C. R., close-up view of eruption taken the same date as figure 1.

The cutaneous eruption soon became universal with a marked exfoliation but without vesiculation or bullae. The mouth and throat lesions became progressively more numerous. A roentgenogram taken March 20, 1934, showed an extensive broncho-pneumonia bilaterally and the condition of the patient became progressively worse, respirations ceasing March 21, 1934.

A limited autopsy was permitted and the principal findings in addition to the universal exfoliative dermatitis were a right-sided cardiac dilatation, bronchopneumonia, acute bilateral purulent bronchitis, and marked subendocardial fatty infiltration.

*Case 2.* E. C., a 45 year old white male, roofer by occupation, was admitted to the University Hospital, May 7, 1937, complaining of a cough, "chest trouble," and a skin eruption. About six weeks prior to admittance to the hospital the patient contracted a cold, accompanied by a temperature of 102°, muscle and joint pains, cough and pain in the chest. Work was attempted after a two week convalescence, but all previous symptoms recurred, especially the productive cough. He was treated by his physician and the medication consisted of six white tablets and eight capsules daily for about two weeks. (This was later found to be phenobarbital one-half grain and ephedrine sulphate capsules three-eighths grain respectively.) Six days before coming to the hospital the temperature rose to 103° F., the general condition became much worse, and a "spotty rash" developed on the extremities, trunk and face, which was rapidly becoming more extensive.

Physical examination showed the patient to be acutely ill with a temperature of 103° F., pulse 120, and respirations 24. He presented an extensive generalized erythematous maculo-papular eruption which spared only the palms, soles and scalp. The patches were penny to palm-sized with a tendency toward confluence, of a reddish-brown to a reddish-purple color, blanched on pressure, and without sharp demarcation fading off into the normal skin. The most marked involvement was seen over the back, the anterior thigh surfaces showing the least. The genitalia were markedly erythematous and edematous with a patchy superficial denudation of the epithelial covering of the scrotum. Numerous vesicles were present about the vermillion and mucous surface of the lips and throughout the oral cavity and pharynx. The cervical glands were enlarged as were the left axillary glands. The heart rate was rapid but there were no murmurs heard nor any irregularity of rate or rhythm. The blood pressure was 124 mm. systolic and 74 mm. diastolic. The left lung base posteriorly was slightly dull to percussion and auscultation revealed coarse râles over both bases and in the axillae, but there was no increased transmission of breath or voice sounds. Tactile fremitus was normal. Percussion and palpation of the abdomen revealed no splenic or liver enlargement. The inguinal glands were olive-sized, discrete, firm and non-tender. The superficial and deep reflexes were active and equal. Rectal examination showed a prostate of normal size and consistency.

Laboratory examination showed the blood Kahn reaction to be negative; urine examination was normal. Tests for iodides and bromides in the urine were negative. A blood count taken on May 7, 1937, showed a normal hemoglobin and red cell count with a white blood count of 17,350. On May 11, 1937, the white cell count had dropped to 7,000 with a differential count of polymorphonuclear leukocytes, 88 per cent, lymphocytes 12 per cent, and further drop was noted on May 13, to 6,000 white blood cells with a similar cell distribution. Sputum examination was negative for acid-fast bacilli and spirochetes. Blood culture showed no growth. Blood non-protein nitrogen was 27.2 mg. per cent. Stereoscopic films taken May 7 revealed a calcareous parenchymatous scar of the right apex, bilateral minimal calcareous peribronchial adenopathy, and residual peritruncal infiltration, left inferior lobe with obliterative pleuritis.

The patient was given frequent colloid baths, intravenous sodium thiosulphate and large amounts of intravenous glucose and normal saline infusions. His chronic respiratory infection was treated with inhalations, expectorants and mild sedatives. The

cutaneous reaction remained stationary until May 10 when new small and large vesicles and bullae appeared on the trunk and extremities. By May 12, the eruption became almost universal, the palms, soles and a small patch on the anterior surface of each thigh remaining uninvolved. Throughout hospitalization the temperature remained septic in character, ranging between 100° and 104° F., and on May 12 definite signs of bronchopneumonia were elicited. The patient became progressively weaker and death occurred May 14, 1937.

An autopsy substantiated the clinical findings. In addition to the bilateral lobular pneumonia and almost universal bullous, ulcerative and exfoliative dermatitis, the findings included an acute diphtheritic laryngitis and esophagitis, and an acute passive congestion and degeneration of all parenchymatous organs.

### COMMENTS

A review of the literature reveals an increasing incidence of reactions from the use of the barbiturates in therapy.

The recorded fatal cutaneous eruptions from phenobarbital therapy are few in number but it is believed numerous others have been observed, allowed to go undiagnosed, or if recognized, mentioned incidentally or not at all in the literature.

The characteristic eruption due to phenobarbital medication in the more severe cases may be differentiated from the maculo-papular eruption due to the basic coal-tar derivatives which do not proceed to the stage of vesiculation and exfoliation.

It is believed that the medical profession as a whole should be aware of the dangers of the indiscriminate use of the barbiturates, and that possible serious reactions may occur when treating patients with repeated daily administrations of the various derivatives of the group.

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# SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNGS; REPORT OF AN ADDITIONAL CASE\*

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INTERSTITIAL emphysema of the lungs following injury or greatly increased intrapulmonary pressure has long been recognized clinically by the appearance of air in the subcutaneous tissues about the neck. The term surgical emphysema has been applied to this condition to distinguish it from vesicular emphysema produced by bronchial obstruction and subsequent dilatation of the pulmonary alveoli. The first description of interstitial emphysema occurring spontaneously, that is, without trauma or greatly increased intrapulmonary pressure, was recorded by Hamman<sup>1</sup> in 1937. He reported six cases and described a new physical sign characteristic of the condition. He emphasized that spontaneous interstitial emphysema is probably commonly overlooked because of the similarity of its symptomatology to that of other well known diseases.

SUMMARY OF CASES OF SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNGS

Case No.	Age	Sex	Occupation	History	Subcutaneous Emphysema	Roentgenogram	Duration of illness
1	51	Male	Physician	Sharp pain in chest for one hour.	Absent	Normal	2 weeks
2	17	Male	Tin worker	Substernal pain, swelling above clavicles, dysphagia, painful breathing for several hours.	Present above both clavicles.	Not done	Less than 4 weeks
3	25	Male	Physician	Pain in left side of chest. Crackling sensation in region of heart.	Absent	Normal	10 days
4	34	Male	Not given	Substernal pain, choking sensation, "noises in heart" 2 hours.	Absent	Small pneumothorax left apex.	2 weeks
5	29	Male	Salesman	Severe pain in left side of chest.	Absent	Small pneumothorax on left.	3 weeks
6	16	Male	Student	Severe pain in right side of chest for ten minutes.	Present above both clavicles.	Air in anterior mediastinum.	18 days
7	27	Male	Laborer	Sharp pain in left side of chest for one hour. Dyspnea, weakness, noise in chest.	Absent	Small pneumothorax on left. Fluoroscopy showed air in anterior mediastinum	3 weeks

The first six cases were reported by Hamman, the seventh is that of the author.

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Since the six cases reported by Hamman no others have been recorded in the literature so far as I have been able to find. His cases are summarized in the table together with an original case.

#### CASE REPORT

A laborer, aged 27, came to the clinic of the Atlanta Tuberculosis Association on July 25, 1938, complaining of a peculiar noise in his chest. About two weeks previously, while rolling an empty wheelbarrow, he had been suddenly seized with a sharp pain in the left side of his chest over his heart. The pain was knife-like in quality and so severe that he thought he was going to faint. Shortly after the onset of pain he felt a sensation of tightness substernally and became short of breath. His companions told him he was pale and blue. On reaching home about an hour later the pain was less intense and he was able to breathe with only slight difficulty. On getting in bed and turning on his left side he experienced a grinding crunching sensation in the region of his heart. Standing at least a yard from the patient, his wife heard what she described as a noise "like the wadding up of paper." This sound was heard by several other members of his family. Aside from the discomfort from the peculiar sensation there was no increase in the pain while the sensation was present. After a day in bed, only slight soreness in the left side of the chest and moderate dyspnea were present. He was able to return to his work as a laborer the following day. The crunching sound and sensation, however, remained, though somewhat abated, until his admission to the clinic. At that time he had no pain but was still short of breath on exertion.

The patient was a rather thin undernourished young white man not appearing ill. There were signs of a small pneumothorax in the left axilla. The area of cardiac dullness was normal in position and extent, the sounds were of good quality with a faint systolic murmur at the apex. On turning the patient on his left side there appeared a crunching, crackling, slapping sound synchronous with the heart beat. The sound was clearly heard with the bare ear a foot from the patient. It was accentuated on expiration and diminished on inspiration, disappearing entirely when the patient turned from the left side.

His temperature was 98.6°; a complete blood count and urinalysis were normal. The blood pressure was 130 systolic, 80 diastolic. The tuberculin test, using first strength (0.01 mg.) Purified Protein Derivative intradermally, gave a moderately positive reaction. A roentgenogram of the chest showed a small area of pneumothorax on the left with about 10 per cent collapse of the lung. Fluoroscopic examination demonstrated several bubbles of air in the tissues between the anterior surface of the heart and the chest wall and between the diaphragm and the pericardium. With the production of the peculiar noise the bubbles of air between the heart and anterior chest wall changed shape with each movement of the heart and lungs.

The patient was given a cough mixture and was put to bed for a week. At the end of this time he reported that the dyspnea and crunching sensation had disappeared. Fluoroscopic examination at this visit was entirely negative. Three weeks after admission to the clinic he returned to work and has felt well since. A roentgenogram taken Sept. 2, 1938, was reported normal.

#### COMMENT

The mechanism by which the air reaches the mediastinum has been postulated by Hamman who wrote:

I am convinced that not infrequently pulmonary alveoli must rupture and air escape into the interstitial tissues of the lung. If only a small amount of air escapes

no symptoms may appear or perhaps only localized pain. This condition may account for some of the many transient pains in the chest of which patients complain and for which no cause can be discovered. If a larger amount of air escapes it may travel along the interstitial bands to the pleura and there form a vesicle; the pleural membrane over the vesicle is stretched and often ruptures. This seems to me the most reasonable explanation for the occurrence of spontaneous pneumothorax. At other times the air spreads along the interstitial bands toward the hilum and escapes into the mediastinum, infiltrating the mediastinal tissues which lie between the heart and anterior chest wall and often escaping into the subcutaneous tissues of the neck. The symptoms then produced are severe and may closely simulate the symptoms of coronary occlusion or of pericarditis.

In cases of spontaneous interstitial emphysema there is a sudden onset of a sharp pain in the chest which may be accompanied by a choking sensation, dyspnea and a feeling of tightness substernally. Occasionally swelling above the clavicles will be noted by the patient. The pain is usually severe at the time of its first appearance, then gradually diminishes in intensity until it disappears, usually within one or two hours after the onset. Often the patient will notice a peculiar crunching noise or sensation in his chest. This phenomenon frequently is present only when a certain posture is assumed and in some cases the pain will be intensified with its appearance. The symptoms of this condition are, as has been pointed out, similar to those seen in a variety of diseases, notably coronary artery disease and pericarditis. In these diseases, however, there is more likelihood of a severe constitutional reaction resulting from myocardial disturbance and shock.

On physical examination one may find subcutaneous emphysema in the neck. The area of cardiac dullness may be diminished in extent or even absent. Signs of a pneumothorax may be present. Often a loud crunching, grinding, crackling sound synchronous with the heart beat can be heard some distance from the chest wall. This sign, first described by Hamman, is characteristic of interstitial emphysema and is unlike the so-called "cardiac knock" or "systolic râles" which are sometimes heard over the heart in cases of pneumothorax or atelectasis. In some cases air may be demonstrated in the mediastinal tissues by fluoroscopic examination or by a roentgenogram.

Once the diagnosis is established the patient may be treated symptomatically and reassured as to the favorable prognosis, for the symptoms soon disappear, leaving him apparently as well as before. When recovery is complete there is no indication to curtail his activities in any way.

*Note:* Since this case was reported another typical case of spontaneous interstitial emphysema has been observed by the author.

#### REFERENCE

1. HAMMAN, LOUIS: Spontaneous interstitial emphysema of the lungs, *Trans. Assoc. Am. Phys.*, 1937, iii, 311-319.

## EDITORIAL

### INTESTINAL STASIS AND MACROCYTIC ANEMIA

IN 1895 Faber<sup>1</sup> in Denmark first called attention to the association of pernicious anemia with a stricture of the small intestine. He postulated that absorption of a poison from the stagnant bowel contents above the stricture was responsible for the anemia. Meulengracht<sup>2</sup> added weight to this theory in 1921 when he found at the autopsy of a case of severe "pernicious anemia" associated with a tuberculous stricture of the ileum that the entire small intestine was heavily infected with bacteria. Comparing his case with five similar cases previously reported he arrived at the following conclusions: (1) pernicious anemia may develop on the basis of benign intestinal strictures; (2) the anemia is probably due to the absorption of hemotoxic substances from the dilated and infected portion of the bowel above the stricture; (3) such cases support the theory of the intestinal origin of cryptogenetic pernicious anemia.

Several years later these clinical observations received experimental support when Seyderhelm<sup>3</sup> and his associates succeeded in simulating the clinical and pathologic picture of stricture anemia in four of ten dogs in which they had produced intestinal strictures at operation. Later Horster<sup>4</sup> added further experimental evidence along the same lines by producing severe anemia associated with indicanuria and hemosiderin deposits in the liver and spleen in dogs with intestinal strictures or blind pouches which he had created at operation. The symptoms cleared up after resection of the blind pouch or stricture.

Seyderhelm was the first to report recovery from pernicious anemia in a patient after resection of an intestinal stricture. He has also recorded two instances of striking improvement in patients with pernicious anemia following the institution of ileostomy to afford better drainage of the bacteria-infested small intestine. Dixon<sup>5</sup> and his associates in this country have observed a similar response to ileostomy in certain patients suffering from pernicious anemia. These observations all fitted in well with Meulengracht's original concept of the etiology of pernicious anemia.

Then with the discovery of liver therapy for pernicious anemia by Minot and Murphy in 1926, soon to be followed by Castle's fundamental observations on the relation of the intrinsic (gastric) and extrinsic (food) factors

<sup>1</sup> FABER, K.: Perniciöse Anämie bei Dünndarmstrikturen, Berlin. klin. Wchnschr., 1897, xxxiv, 643-646. (Case previously published in Danish literature, 1895.)

<sup>2</sup> MEULENGRACHT, E.: Darmstriktur und perniziöse Anämie, Arch. f. Verdauungskr., 1921, xxviii, 216-225.

<sup>3</sup> SEYDERHELM, R., LEHMANN, W., and WICHELS, P.: Intestinale perniziöse Anämie beim Hund durch experimentelle Dünndarmstriktur, Krankheitsforschung, 1927, iv, 263-279.

<sup>4</sup> HORSTER, H.: Experimentelle Therapie bei intestinaler Autointoxication, Ztschr. f. d. ges. exper. Med., 1935, xcv, 514-518.

<sup>5</sup> DIXON, C. F., BURNS, J. G., and GIFFIN, H. Z.: Pernicious anemia following ileostomy, Jr. Am. Med. Assoc., 1925, lxxxv, 17-20.



to the hematopoietic principle contained in liver, the toxic theory gave way to the overwhelming evidence that pernicious anemia was a deficiency disease, or at least a "conditioned deficiency state." However, the exact mechanism of action of the liver principle is still a mystery. The possibility exists that this principle may act, not as a mere building-stone for the proper maturation of the erythrocytes, but conceivably by promoting the detoxification of injurious substances absorbed from the intestinal tract.

In an attempt to examine this hypothesis more carefully, Barker and Hummel<sup>6</sup> have recently reviewed 51 cases of macrocytic anemia in association with intestinal strictures and anastomoses. The macrocytic anemia in these patients differed from so-called idiopathic pernicious anemia in several respects, namely: the presence of free hydrochloric acid in the gastric juice of nearly 50 per cent of the cases, the demonstration of intrinsic factor in the gastric juice of several patients, and the relative infrequency of neurologic manifestations. That the relationship between the macrocytic anemia and the intestinal lesion was more than a coincidental one was definitely established in the six cases in which surgical correction of the intestinal abnormality was followed by disappearance of the anemia without the aid of liver therapy. Other patients in the series responded sufficiently well to liver therapy to render operative interference unnecessary.

The clinical picture presented by this group of cases more closely resembles sprue than true pernicious anemia, yet in those cases in which tests of intestinal absorption were carried out the striking impairment in intestinal absorption so characteristic of sprue was not noted. The anemia seemed to be intimately bound up with stagnation and putrefaction of the contents of the small intestine, either above strictures or in blind loops created by anastomoses. Two possible explanations for the production of the anemia were suggested: (1) the increased bacterial activity in the intestinal tract leads to the destruction of hematopoietic material before it can be assimilated; (2) the increased absorption of hemotoxic products of bacterial putrefaction gives rise to the anemia through the direct action of these toxins on the blood, bone-marrow, or even the liver. It was impossible to determine which of these two mechanisms might be playing the major rôle. At any rate, the anemia could be alleviated either by removing surgically the cause for stagnation or by supplying an excess of the liver principle. If the toxic theory be correct, then "stricture anemia" may be regarded as a condition in which the body is unable to supply sufficiently large amounts of detoxifying principle (liver principle) to neutralize the excess of toxins absorbed. The development of true "idiopathic" pernicious anemia on the other hand might depend upon the failure of the body (through lack of intrinsic factor) to synthesize the detoxifying principle in sufficient amounts to neutralize the toxic substances normally absorbed from an intestinal tract where stagnation is not necessarily a factor.

<sup>6</sup> BARKER, W. H., and HUMMEL, L. E.: Macrocytic anemia in association with intestinal strictures and anastomoses, *Bull. Johns Hopkins Hosp.*, 1939, *lxiv*, 215-256.

## REVIEWS

*Sterility and Impaired Fertility.* By CEDRIC LANE-ROBERTS, M.S., F.R.C.S., F.R.C.O.G., ALBERT SHARMAN, M.D., M.R.C.O.G., KENNETH WALKER, F.R.C.S., B. P. WIESNER, D.Sc., Ph.D., F.R.S.E. with a foreword by the Rt. Hon. LORD HORDER, G.C.V.O., M.D., F.R.C.P. 419 pages; 22.5 × 14.5 cm. Paul B. Hoeber, Inc., New York. 1939. Price, \$5.50.

During the past decade real progress has been made in the study of the physiology of the generative organs and much attention has been given to the consideration of sterility. Indeed, the publications on the scientific and practical aspects of sterility and impaired fertility have been so numerous that it has become difficult for even those especially interested in these subjects to be thoroughly conversant with all the literature. Hence it is that such a comprehensive treatise on these subjects as had been written by Lane-Roberts and his three associate authors should be enthusiastically received by the medical profession.

There are eight chapters to this book but it falls rather naturally into three parts. The first covers the general problem of sterility. The second deals with the part played by the male and emphasizes that in a high percentage of instances it is the husband that is responsible for the lack of offspring. The third part of the book is devoted to the gynecological aspects of sterility.

Considerable attention is given to the chemical and morphological examination of semen. The rôle played by the endocrine glands in the control of the reproductive organs is thoroughly covered but in doing this the authors have not passed over the mechanical factors in sterility.

There are references in the appended bibliography to over three hundred articles on sterility and impaired fertility and an appendix which covers many case reports. The genito-urinary specialist, the gynecologist, the man working in the laboratory on problems related to sterility and the general practitioner can all profit from reading this book.

L. B.

*The Practice of Allergy.* By WARREN T. VAUGHN, M.D. 1st. Ed. 1082 pages; 26.5 × 17.5 cm. The C. V. Mosby Co., St. Louis. 1939. Price, \$11.50.

As usual, Dr. Vaughn has written a scholarly book, demonstrating again his wide knowledge of the subject under consideration. The format of the book is attractive in appearance. There are numerous, excellent illustrations which add materially to the text.

Dr. Vaughn has divided his book into 16 parts. It begins with a section outlining the steps in the development of our present understanding of clinical allergy; the general characteristics of clinical allergy, such as the incidence and the effect of climate and heredity, are considered. The next section is on the physiology of allergy and then in order are presented: allergic diagnoses, diagnosis and treatment of food allergy, food allergens, pollens and pollenosis and other inhalant allergy; bacteria and fungi; entomogenous and percutaneous or diadermal allergy; anaphylactic shock; contact allergy; physical allergy; pharmacology; and last, the allergic diseases.

The section on fungi and the section on food allergies are very complete and should be of great value. The botanical classification of foods is presented and a workable classification of fungi, commonly met with clinically, is also given.

Careful and thorough reading impresses the reviewer again with the vast amount of information upon the subject of allergy that Dr. Vaughn has brought together in this book. However, in certain respects the book leaves a sense of dissatisfaction.

First, the arrangement seems faulty in that certain things are overstressed, perhaps at the expense of others that should receive more attention. As an evidence of this, the leukopenic index is given 17 pages, whereas the discussion of the entire subject of skin testing occupies only 22 pages.

Again, Dr. Vaughn discusses very exhaustively the subject of "Diet Diaries" as a diagnostic step in food allergy, giving the impression that they are most helpful in a considerable percentage of cases. The reviewer's experience with this procedure over a period of years has been much less satisfactory, and hence this section appears to him to be tinged with undue optimism. Furthermore, Dr. Vaughn, in the earlier portions of his book philosophizes a great deal about the subject of allergy, and such speculative material appears of doubtful value in a book offered as a standard text.

In the main, certain methods of approach have been developed for books covering given fields of medicine and these methods are adhered to almost without exception by authors of text books.

In this regard, it is the reviewer's opinion that the best plan for the discussion of the subject of allergy that has been developed to date, is that which first covers the general principles; second, the etiologic groups with a discussion of their group characteristics; and third, the clinical conditions encountered in allergy. In the interest of clarity and uniformity this usual arrangement offers advantages over that adopted by Dr. Vaughn.

As a reference book, "The Practice of Allergy" can be highly recommended; as a text book, emphasizing evenly the different aspects of the subject, it can not be accorded the same warm reception.

H. B.

*Textbook of Pathology—A Correlation of Clinical Observations and Pathological Findings.* By CHARLES W. DUVAL, Professor of Pathology and Bacteriology, Tulane University School of Medicine, Chief Visiting Pathologist, Charity Hospital, New Orleans, and HERBERT J. SCHATTENBERG, Associate Professor of Pathology and Bacteriology, Tulane University School of Medicine, Visiting Pathologist, Charity Hospital, New Orleans. 681 pages, 383 illustrations, 13 colored plates; 25 X 17 cm. D. Appleton-Century Co., Inc., New York. 1939. Price, \$8.50.

This one volume text of Pathology appears as a competitor in a field already well stocked with sound standard works which are being periodically revised. The subtitle of the book may offer an excuse for such a volume, but there is nothing new in the attempt to correlate clinical observations with pathologic findings; in fact, this represents the fundamental purpose of the study of Pathology.

On first opening the book one is confronted with a gaudy unnatural frontispiece and is further discouraged by the inexact and muddled manner of considering the fundamental processes of inflammation and degeneration. It is hoped that the misquotation of Menken's term "Leucotaxine" as leucotoxine is a typographical error. The use of the term tubercular for tuberculous may be excusable in lay usage but appears as a glaring mistake in a medical textbook.

The short chapter on etiology of disease and the host reactions is poorly expressed confusing and too dogmatic. The one page on anaphylaxis confuses rather than elucidates the subject.

The greater portion of the book is devoted to special pathology. The consideration of pathologic processes by systems is more or less conventional. The evaluation of space in regard to subject matter is not in ratio to relative importance. There is an entire chapter of 70 pages on diseases of the cutaneous system with 12 of these devoted to leprosy, while all the diseases of the osseous system are contained in less than 10 pages.

In the important subject of neoplasia there is little attempt at clinical correlation.

The illustrations are plentiful but of mediocre quality. With the present photographic methods there seems little excuse for the drawings, many of which convey little information. A number of the photomicrographs are not representative of the condition; for instance, figure 274, adenoma, appears to be an endometrial hyperplasia; figure 290, carcinoma of the breast (intraductal) shows no clear evidence of malignancy in the field represented. Such inaccuracies seriously threaten the value of the book.

The references are restricted to publications in English and this fault is further emphasized by the fact that they are for the most part outdated.

The concluding chapter on the autopsy may serve as an outline for the student in the preparation of a protocol.

On the whole this book is disappointing.

C. G. W.

*The Care of a Small Rat Colony.* By ROLLAND J. MAIN, Ph.D. 101 pages; 22 × 14.5 cm. C. V. Mosby Co., St. Louis. 1939. Price, \$2.00.

With due emphasis on practical problems Dr. Main tells his experiences with a colony of 750 rats maintained on a restricted budget. He treats such questions as type of rat, equipment, care, and costs, with notes on the making of records and breeding routine. Considerable space is given to the mixing of feed, a necessary procedure when foods are to be tested and one that reduced the cost of dry food to 53 cents per adult rat per year.

As the apologia intimates, however, this book will not completely fill the needs of the average worker since it deals almost exclusively with the requirements of the author's laboratory. A procedure for vitamin D assay is given in detail. The inclusion of more data on fertility and mortality would have made the book more useful though somewhat less readable.

This book adequately describes the fundamental care necessary for raising a standard experimental rat.

E. G. B.

## COLLEGE NEWS NOTES

### GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged:

#### *Books*

Dr. William David Sansum, F.A.C.P., and Dr. Alfred E. Koehler (Associate), both of Santa Barbara, Calif., "A Manual for Diabetic Patients."

#### *Reprints*

Dr. Stanton T. Allison (Associate), New York, N. Y.—1 reprint;  
Col. Alexander T. Cooper, F.A.C.P. (MC), U. S. Army—1 reprint;  
Dr. Robert H. Felix (Associate), Lexington, Ky.—1 reprint;  
Dr. George Ginsberg (Associate), Hoboken, N. J.—1 reprint;  
Dr. A. Allen Goldbloom, F.A.C.P., New York, N. Y.—3 reprints;  
Dr. Harold I. Gosline (Associate), Ossining, N. Y.—19 reprints, 1 translation and 1 bulletin;  
Dr. Augustus A. Hall, F.A.C.P., Columbus, Ohio—3 reprints;  
Dr. Arthur O. Hecker (Associate), Woodville, Pa.—1 reprint;  
Dr. Charles S. Higley, F.A.C.P., Cleveland, Ohio—1 reprint;  
Dr. Edward Sandling King, F.A.C.P., Wake Forest, N.C.—1 reprint;  
Dr. Rudolph Leiser (Associate), Eloise, Mich.—1 reprint;  
Dr. C. Ray Lounsberry, F.A.C.P., San Diego, Calif.—1 reprint;  
Dr. Ralph Waldo Mendelson, F.A.C.P., Albuquerque, N. M.—1 reprint;  
Dr. Michael A. Ogden, F.A.C.P., New Orleans, La.—4 reprints;  
Dr. Richard E. Olsen, F.A.C.P., Pontiac, Mich.—5 reprints;  
Dr. William K. Purks, F.A.C.P., Vicksburg, Miss.—1 reprint;  
Dr. Harold L. Rakov (Associate), Kingston, N. Y.—1 reprint;  
Dr. Alexander F. Robertson, Jr., F.A.C.P., Staunton, Va.—1 reprint;  
Dr. Rafael Rodriguez-Molina, F.A.C.P., San Juan, P. R.—1 reprint;  
Dr. Albert Soiland, F.A.C.P., Los Angeles, Calif.—7 reprints;  
Dr. Leon J. Solway, F.A.C.P., Toronto, Ont., Canada—2 reprints;  
Dr. Frederick R. Taylor, F.A.C.P., Hight Point, N. C.—1 reprint;  
Dr. Myer Teitelbaum (Associate), Detroit, Mich.—1 reprint;  
Dr. Morris M. Weiss, F.A.C.P., Louisville, Ky.—3 reprints;  
Dr. Edward E. Woldman (Associate), Cleveland, Ohio—1 reprint;  
Dr. Bernard L. Wyatt, F.A.C.P., Tucson, Ariz.—1 reprint.

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### 1940 PROGRAM OF POSTGRADUATE COURSES

The American College of Physicians' Committee on Postgraduate Education and the Board of Regents announce the following special limited Postgraduate Courses, to be given preceding the 24th Annual Session of the College in Cleveland, April 1-5, 1940:

#### *Ann Arbor, Mich.*

No. 1—General Medicine—University of Michigan, Dr. Cyrus C. Sturgis, Director; March 18-30.

*Detroit, Mich.*

No. 2—Medicine in Industry—Henry Ford Hospital; Dr. Frank Sladen, Director; March 25–30.

*New York City*

No. 3—Allergy—Cornell University Medical College; Dr. Robert A. Cooke, Director; March 18–30.

*Columbus, Ohio*

No. 4—Hematology—Ohio State University; Dr. Charles A. Doan, Director; March 25–30.

*Iowa City, Iowa*

No. 5—Circulatory Diseases—State University of Iowa; Dr. Fred M. Smith, Director; March 25–30.

This is the third year of this activity by the College. The College has been able to make these courses available to its Fellows and Associates at minimum cost, because the College itself assumes full responsibility for promotion, advertising, printing and registration, as its contribution to its members.

The registration fee for each two-weeks course will be \$40; for each one-week course, \$20. One-half of the registration fee will be payable at time of registration and the balance shall be paid not later than March 12, a week in advance of the opening of the courses. The advance payment may be refunded by the College to any registrant who, for adequate reason, is unable to pursue the course, provided notice of withdrawal is registered ten days in advance of the opening of the courses.

Full description of the courses and other announcements appear in a special Bulletin, distributed to members. The number of admissions to each course will necessarily be restricted according to facilities. Registrations will be assigned in order of receipt.

The College will record all registrations with the respective institutions offering courses and will directly reimburse those institutions for each student-physician at the specified registration fee. A Matriculation Card will be sent each registrant from the College office when the fee has been paid in full.

## EDUCATIONAL FILMS

It has been suggested by some members of the College that as a part of its program of aid to postgraduate medicine the College might well interest itself in the possible extension of the utilization of educational medical films dealing with various aspects of internal medicine. To assist the College in collecting data on the number of such films now in use, all our members are asked to forward to the President, Dr. O. H. Perry Pepper, at 4200 Pine St., Philadelphia, any and all information they may possess concerning such films, including their subject matter and the address of their owners.

## REGIONAL MEETING OF KENTUCKY MEMBERS

A regional meeting of Fellows and Associates of the American College of Physicians residing in Kentucky was held at Louisville, December 14, 1939, under the Governorship of Dr. Chauncey W. Dowden. The afternoon was devoted to the following program at the Louisville City Hospital:

1. Staphylococcemia Cured with Sulphapyridine (with report of a case). Dr. Frank M. Stites, F.A.C.P.

2. Some Observations on Diphtheria Immunizations in Louisville. Dr. Hugh R. Leavell, F.A.C.P.
3. Banti's Syndrome Due to Hodgkin's Disease. Dr. Harold Gordon, F.A.C.P.
4. Case Presentation. Dr. Harry S. Frazier, F.A.C.P.
5. Clinico-Pathological Conference. Drs. John Walker Moore, F.A.C.P. and Aura J. Miller, F.A.C.P.
6. Prostigmin in Myasthenia Gravis. Dr. J. J. Moren, F.A.C.P.

Dr. Sam A. Overstreet, F.A.C.P., was in charge of arrangements.

In the evening a Dinner was held at the Pendennis Club in honor of Dr. O. H. Perry Pepper, President of the College, who delivered an address.

Out of an active membership of about 54 members in Kentucky, 50 were present at the scientific meeting and at the dinner. Every member of the College from Louisville was in attendance. It was generally agreed that this was the most successful regional meeting the Kentucky members have yet conducted. For 1940 the Kentucky Meeting will be held at Lexington.

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#### REGIONAL MEETING OF KANSAS MEMBERS

A regional meeting of the Fellows and Associates of the College residing in Kansas was held at Wichita, November 18, 1939, under the Governorship of Dr. Thomas T. Holt. An all-day session was held, starting at 10:30 in the morning and continuing after dinner in the evening. The program was as follows:

- 10:30 a.m. Pathological Conference, St. Francis Hospital. Dr. C. A. Hellwig, Wichita, Kansas.
- 1:00 p.m. "The Histamine Test in Arterial Hypertension." Dr. Maurice Snyder, Salina, Kansas.
- "A New Therapeutic Agent in the Treatment of Diarrhea." Dr. Harold H. Jones, F.A.C.P., Winfield, Kansas.
- "Physiology, Relative to the Kidney." Dr. Earl L. Mills (Associate), Wichita, Kansas.
- "An Investigation of Important Factors Bearing upon the Specificity and Interpretation of Serological Tests Used in the Diagnosis of Syphilis." Dr. N. P. Sherwood, Professor of Bacteriology, Lawrence, Kansas.
- "Electroencephalography." Dr. Norman Reider (Associate), Topeka, Kansas.
- "Lymphosarcoma of the Epidural Space." Dr. Ralph L. Drake (Associate), Wichita, Kansas.
- "Report on Results of Treatment with Metrazol." Dr. Ralph M. Fellows, F.A.C.P., Osawatomie, Kansas.
- "Insulin Therapy in Mental Diseases." Dr. D. V. Conwell, F.A.C.P., Halstead, Kansas.
- 6:30 p.m. Dinner.
- "Endocrines and Vitamines." Dr. J. S. Hughes, Professor of Biochemistry, Manhattan, Kansas.
- "What the Clinician Should Know About Edema." Dr. P. M. Krall (Associate), Kansas City, Kansas.

## PUERTO RICAN MEMBERS' MEETING

On the night of December 12 the members of the Puerto Rico Chapter of the American College of Physicians gave a Dinner in honor of Dr. Richard A. Kern, F.A.C.P., of the University of Pennsylvania, who was visiting Puerto Rico as a guest of honor of the Puerto Rico Medical Association, and who addressed the members of the Association on several occasions during the celebration of their annual scientific assembly. The following Fellows were present at the Dinner:

Dr. Ramón M. Suárez,  
Dr. O. Costa Mandry,  
Dr. Enrique Koppisch.

The following Associates were also present:

Dr. Antonio Ortiz,  
Dr. Luis Morales,  
Dr. Carlos Muñoz McCormick,  
Dr. M. de la Pila Iglesias,  
Dr. Juan Sabater,  
Dr. Francisco Landron.

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At the meeting of the House of Delegates of the Puerto Rico Medical Association on December 9, Dr. O. Costa Mandry, F.A.C.P., was elected President of the Puerto Rico Medical Association for the year 1940.

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Dr. Carl V. Weller, F.A.C.P., Professor of Pathology and Chairman of the Department of Pathology, University of Michigan Medical School, is serving as President of the American Association of Pathologists and Bacteriologists.

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Dr. Ralph O. Clock, F.A.C.P., Scarsdale, N. Y., was the author of six articles published in Surgery, Gynecology and Obstetrics during the years 1933 to 1938, embodying the results of his research studies on the sterility of surgical catgut sutures. Dr. Clock emphasized the need of adequate control of suture sterility in the United States and advocated that the Food and Drug Administration of the United States Department of Agriculture set up the necessary equipment and personnel for conducting the work of testing the sterility of catgut sutures in an impartial manner. Beginning January 1, 1940, the bacteriological test proposed by Dr. Clock became official through its adoption in the United States Pharmacopoeia as a standard, under the title, "Tests for the Sterility of Solids."

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The Dallas Academy of Internal Medicine was recently organized and Dr. D. W. Carter, Jr., F.A.C.P., elected President. The first meeting of the Academy was held recently, addressed by Dr. George Herrmann, F.A.C.P., Professor of Medicine at the University of Texas, as the guest speaker. Among members of the new Academy appeared the names of the following College Fellows, all of Dallas:

Dr. R. W. Baird, Dr. R. M. Barton, Dr. C. Frank Brown, Dr. D. W. Carter, Jr., Dr. C. M. Grigsby, Dr. R. B. McBride, Dr. W. H. Potts, Jr., Dr. W. G. Reddick, Dr. Sam Shelburne, Dr. R. M. Smith, Dr. J. S. Sweeney, Dr. George Underwood, Dr. H. M. Winans.

The following Associates are also listed in the membership:

Dr. E. P. Leeper, Dr. M. Hill Metz, Dr. M. B. Whitten.



The California Sanatorium Association held its Annual Meeting at the Wish-I-Ah Sanatorium, Fresno County, on November 11, 1939, under the Presidency of Dr. Harold Guyon Trimble, F.A.C.P., of Oakland. Among speakers on the program were:

Dr. Chesley Bush, F.A.C.P., Livermore, "Report on American Trudeau Society reorganization"; Dr. E. P. Smart, Associate, "What should be the details of contagious technic used on a tuberculosis ward by the attending nurses"; Dr. Charles L. Ianne, F.A.C.P., San Jose, "Is the presence of a negative tuberculin reaction desirable in employees who are going to work on tuberculosis wards"; Dr. F. M. Pöttinger, Sr., F.A.C.P., Monrovia, "Therapeutic Use of Tuberculin."

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Dr. R. M. Lymburner, F.A.C.P., Hamilton, Ontario, Canada, addressed the Grey County Medical Society, at Owen Sound, Ontario, November 8, on "Heart Failure and Its Therapeutic Management"; on November 22, Dr. Lymburner addressed the Huron County Medical Society at Seaforth, Ontario, on "Principles and Treatment of Congestive Heart Failure."

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Dr. Richard M. Burke (Associate), Clinton, Okla., has been appointed Superintendent of the Western Oklahoma Tuberculosis Sanatorium.

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Dr. Edwin Chester Swift, F.A.C.P., Jacksonville, Fla., was elected 1st Vice President, and Dr. Arthur Jones Logie (Associate), Jacksonville, Fla., was elected 2nd Vice President of the Florida East Coast Medical Association at its Twelfth Annual Meeting held at Ponte Vedra, Fla., on November 10-11, 1939.

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Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J., spoke on November 20, 1939, on "Recent Trends in the Treatment of Coronary Heart Disease" at the Fourth Annual Series of Louis Adler Lectures on Cardiology, sponsored by the Medical Board of the Manhattan General Hospital.

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Dr. Morris M. Weiss, F.A.C.P., Louisville, Ky., addressed the Fourth Annual Meeting of the Gulf Coast Clinical Society in Mobile, Ala., on October 27, 1939, on "The Treatment of Coronary Disease."

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Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill., spoke on "Inhalant Allergy: Recent Experiences" at a meeting of the Kings County Medical Society and the Academy of Medicine of Brooklyn, at Brooklyn, N. Y., on December 19, 1939.

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Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, Md., spoke at a combined meeting of the Bradford County and Tioga County Medical Societies held at Troy, Pa., November 28, 1939, on "Diagnosis of Operable Chest Conditions."

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Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., conducted the Fifth Seminar of 1939 before the Lycoming County Medical Society, Williamsport, Pa., November 24, 1939, on "Vitamins and Food Values in Health and Disease."

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Dr. Carlos E. Fallon (Associate), Newburgh, N. Y., was appointed assistant attending physician in the Gastroenterology Department of the New York University College of Medicine Clinic on December 12, 1939.

The Council of the New York Academy of Medicine plans to hold their Thirteenth Graduate Fortnight, October 14-25, 1940.

Under the Presidency of Dr. Louis H. Bauer, F.A.C.P., Hempstead, N.Y., the Second District Branch of the Medical Society of the State of New York held its 33rd Annual Meeting, November 16, 1939. Among those to present symposia were the following:

Dr. Henry M. Moses, F.A.C.P., Brooklyn, N. Y., "Neoplasms of the Chest";

Dr. Carl H. Greene, F.A.C.P., Brooklyn, N. Y., "Differential Diagnosis Between Lung Tumors and Chronic Inflammatory Disease of the Lungs";

Dr. Foster Murray, F.A.C.P., Hempstead, N. Y., "Early Clinical Diagnosis";

Dr. Willard J. Davies, F.A.C.P., Rockville Centre, N. Y., "Correlation of Roentgen Ray with Clinical Findings";

Drs. James C. Walsh, F.A.C.P., Farmingdale, N. Y., and Edwin P. Kolb, F.A.C.P., Holtsville, N. Y., "Medical Management Including Sanatorium Care."

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The University of North Carolina opened a new building for The School of Medicine and The Division of Public Health at Chapel Hill, N. C., Monday, December 4, 1939. Among those who participated in the opening exercises were:

Dr. William deB. MacNider, F.A.C.P.

Dr. I. H. Manning, F.A.C.P.

Dr. C. C. Carpenter, F.A.C.P., Wake Forest, N. C.

Dr. W. C. Davison, F.A.C.P., Durham, N. C.

An address on "The Making of a Clinician" was given by Dr. David Riesman, F.A.C.P., Philadelphia, Pa., and an address on "The Old Medical School of the University—Dr. Richard Henry Whitehead, Dr. Charles Staples Mangum" was given by Dr. James K. Hall (Associate), Richmond, Va.

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Dr. George Ginsberg (Associate), Hoboken, N. J., read a paper entitled "Results with the Prolonged Use of Protamine Zinc Insulin in the Treatment of Diabetes Mellitus," at the Second Fall Clinical Conference of the Medical Society of New Jersey, held at Jersey City, N. J., November 9-10, 1939.

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The New Jersey Gastro-Enterological Society, at its Annual Meeting, December 4, 1939, in Newark, N. J., elected Dr. Manfred Kraemer, F.A.C.P., Newark, President, and Dr. Hyman I. Goldstein (Associate), Camden, Vice President.

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Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, was one of four to whom the first award of the National Canners Association was made on November 20, 1939, "for signal service to the canning industry and to the public health in the discovery of methods leading to the prevention of botulism and in the development of the canning technic relative thereto."

---

Dr. Leslie M. Smith, F.A.C.P., El Paso, Texas, who is now President of the Texas Dermatological Society, recently took office as President of the El Paso County Medical Society for the year 1940.

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Dr. Eugene M. Landis, F.A.C.P., University, Va., spoke at a recent meeting of the University of Virginia Medical Society on "Kidney Extracts and Hypertension." Later, Dr. Landis spoke at the 24th Postgraduate Clinic, sponsored by the

University Medical School, on "Pathological Physiology of Human Hypertension" and at the Roanoke Academy of Medicine on "Hypertension."

---

Colonel J. E. Ash, F.A.C.P., Curator, Army Medical Museum, Washington, D. C., was one of the guest speakers at the meeting of the Southeastern Branch Society of the American Urological Association at Biloxi, Miss., December 8-9.

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Dr. Russell H. Oppenheimer, F.A.C.P., Emory University, who was formerly the College Governor for the State of Georgia, was recently installed as President of the Association of American Medical Colleges.

---

Among the guest speakers at the Third Annual Session of the Atlanta Graduate Medical Assembly were Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.; Dr. Wm. E. Chamberlain, F.A.C.P., Philadelphia, Pa.; and Dr. Philip S. Hench, F.A.C.P., Rochester, Minn.

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Dr. M. E. Winchester, F.A.C.P., Brunswick, Ga., spoke on "Special Administrative Problems of the County Health Officer" at a recent meeting of the International Society of Medical Health Officers, held in Pittsburgh, Pa.

---

Dr. Charles W. Dunn (Associate), Philadelphia, Pa., led a round-table discussion on "Endocrine Problems of Childhood" at the annual meeting of the Virginia Pediatric Society.

---

Among the speakers at a joint meeting of the Neuropsychiatric Society of Virginia and the North Carolina Neuropsychiatric Association were the following:

Dr. David C. Wilson, F.A.C.P., University, Va.—"The Present Status of Our Understanding of Convulsive Disorders";

Dr. R. Finley Gayle, Jr., F.A.C.P., Richmond, Va.—"The Treatment of Parkinsonism with a Preparation of Belladonna Root";

Dr. J. K. Hall (Associate), Richmond, Va.—"The Language-Barrier in Depressed States."

---

Dr. William B. Porter, F.A.C.P., Richmond, Va., has been elected President of the American Clinical and Climatological Association.

---

Dr. Samuel A. Levine, F.A.C.P., Boston, Mass., has been awarded the 1939 Gold Medal for distinguished medical achievements, by the Phi Lambda Kappa Fraternity, at their Convention, held at Park Central Hotel, New York, on January 1, 1940.

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Dr. Wingate M. Johnson, F.A.C.P., Winston-Salem, N. C., has been appointed Editor of the recently established North Carolina State Medical Journal.

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Dr. E. A. Hines, F.A.C.P., Seneca, S. C., was reelected President of the Piedmont Postgraduate Clinical Assembly and Dr. Kenneth M. Lynch, F.A.C.P., Charleston, S. C., who is the College Governor for this state, was elected a Vice-President.

---

Dr. Conley H. Sanford, F.A.C.P., Memphis, Tenn., has been recently made Professor and Head of the Department of Medicine of the University of Tennessee Col-

lege of Medicine to succeed Dr. James B. McElroy, F.A.C.P., who resigned because of ill health.

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Dr. Ernest Kelley, F.A.C.P., Omaha, Nebr., has been appointed Head of the Department of Nervous and Mental Diseases at the Creighton University School of Medicine.

---

Dr. David P. Barr, F.A.C.P., St. Louis, Mo., gave an address at the Cornell University Medical College December 13 on "The Nature of Obesity."

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The following Fellows of the College participated in the program of scientific lectures sponsored by the College of Physicians of Philadelphia:

Dr. O. H. Perry Pepper (President, A.C.P.), Philadelphia, Pa.—"Medical Problems of Advancing Age";

Dr. Howard T. Karsner, Cleveland, Ohio—"Certain Ovarian Tumors Associated with Sexual Endocrine Dysfunction."

---

Dr. Joseph McFarland, Philadelphia, Pa., will give a lecture on "The Pathological Diagnosis of Cancer in Man" on April 3, and Dr. William Edward Chamberlain, Philadelphia, Pa., will give a lecture on "The X-Ray as an Aid in Diagnosis" on April 12.

---

Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio, who is Vice President of the Section on Medical Sciences of the American Association for the Advancement of Science, delivered an address on "The Physiology of Coronary Blood Flow" at their meeting in Columbus, Ohio, December 27-30.

---

Dr. Irving Wright was the guest lecturer of the Chicago Medical Society on December 20. The subject was "Arteriosclerosis Obliterans; Its Modern Conception of Its Social Significance, Diagnosis and Treatment."

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Among physicians taking part in the instruction in the Illinois State Medical Society's Postgraduate Conference at Champaign, Ill., December 7, were:

Dr. Francis E. Senear, F.A.C.P., Chicago—"The Treatment of Athlete's Foot and Other Fungus Infections of the Skin."

Dr. Robert A. Black, F.A.C.P., Chicago—"The Treatment of Common Ailments in Children."

Dr. James H. Hutton, F.A.C.P., Chicago—"The Management of the Male and Female Climacteric."

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Dr. Nathan B. Van Etten, F.A.C.P., New York City, President-Elect of the American Medical Association, delivered an address on "An American Health Program" at the sesquicentennial celebration of the Medical Society of South Carolina at Charleston on December 5.

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Dr. William S. McCann, F.A.C.P., Rochester, N. Y., addressed the Kansas City (Mo.) Academy of Medicine, December 15, on "Modern Trends in the Study of Kidney Disease."

Dr. William W. Graves, F.A.C.P., Professor and Director of the Department of Neuropsychiatry, St. Louis University School of Medicine, was recently honored by the St. Louis Medical Society with a certificate of merit and a gold medal. The award was made in recognition of work by Dr. Graves which "resulted in new approaches to the qualitative evaluation of inherited variations in relation to the inherited qualities of human constitution, expressed in inherited predisposition to health or disease, and in inherited capacity for education, for adaptability and for longevity."

---

Dr. Warfield T. Longcope, F.A.C.P., Baltimore, was recently elected President of the Board of Scientific Directors of the Rockefeller Institute for Medical Research.

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Among speakers at the Sixth Conference of Southern Pathologists, held at Memphis, November 20, were:

Dr. William R. Mathews, F.A.C.P., Shreveport—"The Aspiration Biopsy."

Dr. Charles W. Duval, F.A.C.P., New Orleans—"Teaching of Pathology and Bacteriology as One Subject Matter."

Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C.—"The Present Day Status of Clinical Pathology and Problems of the Clinical Pathologist."

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Under the Presidency of Dr. Raymond G. Taylor, F.A.C.P., Los Angeles, the Radiological Society of North America held its annual meeting at Atlanta, December 11-15, 1939. The program was divided among refresher courses for two hours each morning, general sessions the balance of the morning and sessions for diagnostic and therapeutic subjects in the afternoons.

---

Dr. Frederick T. Lord, F.A.C.P., Clinical Professor of Medicine Emeritus of Harvard Medical School, Boston, delivered the fifth annual John W. Bell Tuberculosis Lecture before the Hennepin County Medical Society at Minneapolis on December 4, his subject being "The Clinical Aspects and Diagnosis of Pulmonary Lesions."

---

Dr. W. Laurence Whittemore, F.A.C.P., and Dr. James R. Lisa, F.A.C.P., both of New York City, are members of a committee in charge of work at the City Hospital on Welfare Island in connection with a newly installed special chamber for experiments in cryotherapy, or the "frozen sleep" method of treating cancer.

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Lt. Col. William D. Fleming, F.A.C.P., M.C., U.S. Army, Edgewood Arsenal, Md., addressed the Philadelphia County Medical Society, November 27, on "Medical Aspects of Chemical Warfare."

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Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio, has been elected President of the Central Society for Clinical Research.

---

Dr. Thomas T. Mackie, F.A.C.P., New York City, has been made President-Elect of the American Society of Tropical Medicine.

---

Dr. William C. Menninger, F.A.C.P., Topeka, Kan., has been elected Secretary-Treasurer of the Central Neuropsychiatric Association.

## NEW ELECTIONS TO COLLEGE MEMBERSHIP

At a meeting of the Board of Regents December 17, 1939, at the headquarters building, Philadelphia; the following candidates were regularly elected to the class indicated:

## ELECTIONS TO FELLOWSHIP

December 17, 1939

*Fellowship Candidates**Sponsors*

## ALABAMA

Seale Harris, Jr., Birmingham

John B. Youmans, Groesbeck Walsh, Fred Wilkerson

William Lindsay Miller, Gadsden

J. Harold Watkins, Seale Harris, Fred Wilkerson

## CALIFORNIA

Richard Donald Evans, Los Angeles

B. O. Raulston, Arthur Stanley Granger, James F. Churchill

Donald E. Griggs, Los Angeles

R. Manning Clarke, Percy T. Magan, James F. Churchill

Eberle Kost Shelton, Los Angeles

Fred B. Clarke, F. M. Pottenger, James F. Churchill

Elliott Plummer Smart, Murphys

E. W. Hayes, Sidney J. Shipman, Ernest H. Falconer

Edward Kupka, Olive View

F. M. Pottenger, Carl R. Howson, James F. Churchill

Walter Cyril Nalty, San Fernando

Charles M. Griffith, Bryan M. Riley, James F. Churchill

Albert Howell Elliot, Jr., Santa Barbara

Hilmar O. Koefod, Harry E. Henderson, James F. Churchill

Russell Lowell Sands, Santa Monica

Roland Cummings, S. M. Alter, James F. Churchill

## CONNECTICUT

Ralph Lawrence Gilman, Storrs

G. Gardiner Russell, Otto G. Wiedman, Francis G. Blake, Charles H. Turkington

## DISTRICT OF COLUMBIA

John A. Reisinger, Washington

John Minor, Thomas S. Lee, Wallace M. Yater

Robert Lomax Wells, Washington

W. Cabell Moore, Henry C. Macatee, Wallace M. Yater

## MEDICAL CORPS, U. S. ARMY

James Carre Magee, Washington, D. C.

William L. Sheep, Joseph R. Darnall, Wallace M. Yater

Frank Wiley Wilson, Fort Benning, Ga.

C. R. Reynolds

## FLORIDA

John Webster Merritt, Jacksonville

R. H. McGinnis, Louie Limbaugh, T. Z. Cason

## GEORGIA

Mark Stovall Dougherty, Jr., Atlanta

Allen H. Bunce, Russell H. Oppenheimer, Glenville Giddings

William Rudy Minnich, Atlanta

H. C. Sauls, Carter Smith, Glenville Giddings

Thomas Fort Sellers, Atlanta

Guy G. Lunsford, Joe P. Bowdoin, Glenville Giddings

William Hugh Trimble, Atlanta

Hal M. Davison, Trimble Johnson, Glenville Giddings

James Fletcher Hanson, Macon

Alvin E. Siegel, J. D. Applewhite, Glenville Giddings

Thomas Llewellyn Ross, Jr., Macon

T. E. Rogers, Stewart R. Roberts, Glenville Giddings

*Fellowship Candidates*

William Pickens Harbin, Jr., Rome

Charles Henry Sprague, Boise

Thomas Austin Starkey, Beardstown

M. Herbert Barker, Chicago

John Harold Mills, Chicago

Walter Lincoln Palmer, Chicago

Eugene Solomon Talbot, Chicago

Michael Zeller, Chicago

Richard Hale Young, Evanston

Harry Willard Shuman, Rock Island

Villairs Thomas Austin, Urbana

Charles Hilbert Drenckhahn, Urbana

Noble Pierce Sherwood, Lawrence

Arthur Joseph Revell, Pittsburg

James Graves Stewart, Topeka

Marion Force Beard, Louisville

Archibald Donaldson Kennedy, Louisville

Frank Anthony Simon, Louisville

Woodford Bates Troutman, Louisville

Grace Arabel Goldsmith, New Orleans

Stanley George Wolfe, Shreveport

Donald Howard Daniels, Portland

Richard Sylvester Hawkes, Portland

Alan Bernstein, Baltimore

Ernest Samuel Cross, Baltimore

Francis Wilcox Gluck, Baltimore

*Sponsors*

Trimble Johnson, Joseph Yampolsky, Glenville Giddings

## IDAHO

Harry A. Collins, Edward W. Anderson, Tom B. Throckmorton

## ILLINOIS

F. G. Norbury, Harold Swanberg, Samuel E. Munson

Lowell D. Snorf, N. S. Davis, III, James G. Carr

Josiah J. Moore, Frederick O. Fredrickson, James G. Carr

Laurence E. Hines, N. S. Davis, III, James G. Carr

J. Roscoe Miller, Arthur E. Mahle, James G. Carr

William H. Welker, Leon Unger, James G. Carr

J. Roscoe Miller, Arthur E. Mahle, James G. Carr

Hugh A. Beam, C. D. Mercer, Samuel E. Munson

E. M. Stevenson, Gerald M. Cline, Samuel E. Munson

E. M. Stevenson, Gerald M. Cline, Samuel E. Munson

## KANSAS

Henry N. Tihen, Fred J. McEwen, Thomas T. Holt

William C. Menninger, Ralph M. Fellows, Thomas T. Holt

William C. Menninger, Philip W. Morgan, Thomas T. Holt

## KENTUCKY

J. Murray Kinsman, J. Richard Gott, Jr., C. W. Dowden

H. V. Noland, J. Murray Kinsman, C. W. Dowden

J. Murray Kinsman, Sam A. Overstreet, C. W. Dowden

Virgil E. Simpson, Arthur Clayton McCarty, C. W. Dowden

## LOUISIANA

John H. Musser, Philip H. Jones, J. E. Knighton

Clarence H. Webb, M. D. Hargrove, J. E. Knighton

## MAINE

E. W. Gehring, E. R. Blaisdell, E. H. Drake  
Harry S. Emery, E. R. Blaisdell, E. H. Drake

## MARYLAND

Louis P. Hamburger, Thomas P. Sprunt, Henry M. Thomas, Jr.

Thomas P. Sprunt, Louis Hamman, Henry M. Thomas, Jr.

Walter A. Baetjer, Sydney R. Miller, Henry M. Thomas, Jr.

*Fellowship Candidates*

Lewis Perkins Gundry, Baltimore  
 Harold Raymond Peters, Baltimore  
 David Tenner, Baltimore  
 Samuel Whitehouse, Baltimore  
 Perry Franklin Prather, Hagerstown

*Sponsors*

T. Nelson Carey, William S. Love, Jr., Henry M. Thomas, Jr.  
 Thomas P. Sprunt, Harvey G. Beck, Henry M. Thomas, Jr.  
 William S. Love, Jr., J. Sheldon Eastland, Henry M. Thomas, Jr.  
 Paul W. Clough, Thomas P. Sprunt, Henry M. Thomas, Jr.  
 Victor F. Cullen, R. S. Stauffer, Henry M. Thomas, Jr.

## MASSACHUSETTS

Earle MacArthur Chapman, Boston  
 Greene Smith FitzHugh, Boston  
 James Carlin McAdams, Fall River

F. Dennette Adams, B. H. Ragle, William B. Breed  
 Maurice Fremont-Smith, Robert S. Palmer, William B. Breed  
 William Mason, Charles C. Wolferth, William B. Breed

## MICHIGAN

Herman Marvin Pollard, Ann Arbor  
 Louis John Bailey, Detroit  
 Nicola Gigante, Detroit  
 John Doyle Littig, Kalamazoo  
 Richard Ellsworth Olsen, Pontiac

Arthur C. Curtis, Herman H. Riecker, Henry R. Carstens  
 Richard Campbell Connelly, Robert Conrad Moehlig, Henry R. Carstens  
 P. L. Ledwidge, Edward D. Spalding, Henry R. Carstens  
 Arthur C. Curtis, Cyrus C. Sturgis, Henry R. Carstens  
 Harold R. Roehm, George A. Sherman, Henry R. Carstens

## MINNESOTA

Charles Everard Lyght, Northfield

J. A. Myers, Elmer L. Sevringhaus, E. V. Allen

## MISSOURI

Sim Fields Beam, St. Louis  
 Kenneth Franklin Glaze, St. Louis  
 Harold Gould Newman, St. Louis

Walter Baumgarten, Anthony B. Day, A. C. Griffith  
 Walter Baumgarten, Charles Hugh Neilson, A. C. Griffith  
 Howard A. Rusk, Walter Baumgarten, A. C. Griffith

## MONTANA

Malcolm Duncan Winter, Miles City

Allen R. Foss, John Paul Ritchey, Louis H. Fligman (deceased)

## NEBRASKA

Chester Quay Thompson, Omaha

Rodney W. Bliss, Lynn T. Hall, Warren Thompson

## NEW JERSEY

Thomas Krapfel Lewis, Camden  
 Jerome George Kaufman, Newark  
 Sigurd Walter Johnsen, Passaic

Ralph K. Hollinshed, Hilton S. Read, George H. Lathrope  
 Aaron E. Parsonnet, Edgar Mayer, George H. Lathrope  
 Manfred Kraemer, George Milton Knowles, George H. Lathrope



*Fellowship Candidates**Sponsors*

## NEW YORK

George William Weber, Albany  
 James Arthur Buchanan, Brooklyn  
 George B. Dorff, Brooklyn  
 Stuart L. Vaughan, Buffalo  
 Cornelius Packard Rhoads, New York  
 Ralph Horton, Oneonta  
 James Murray Flynn, Rochester  
 Clement Joseph Handron, Troy  
 Alson Joye Hull, Troy  
 Clarence Orion Cheney, White Plains

F. W. Holcomb, James F. Rooney, C. F. Tenney  
 George Forbes, Philip I. Nash, C. F. Tenney  
 Irving J. Sands, Harry R. Litchfield, C. F. Tenney  
 A. H. Aaron, Clayton W. Greene, Nelson G. Russell  
 Thomas T. Mackie, James Alex. Miller, C. F. Tenney  
 J. K. Deegan, J. Burns Amberson, Jr., C. F. Tenney  
 John M. Swan, C. Clyde Sutter, Nelson G. Russell  
 Crawford R. Green, James F. Rooney, C. F. Tenney  
 Crawford R. Green, Stephen H. Curtis, C. F. Tenney  
 Charles A. McKendree, Willard C. Rappleye, C. F. Tenney

## NORTH CAROLINA

Walter Reece Berryhill, Chapel Hill  
 Thomas Williams Baker, Charlotte  
 Sidney Ferring LeBauer, Greensboro  
 Erle Bulla Craven, Jr., Lexington  
 George Erick Bell, Wilson

William de B. MacNider, Soma Weiss, Charles H. Cocke  
 Edward J. Wannamaker, T. Preston White, Charles H. Cocke  
 Frederick R. Taylor, D. Waldo Holt, Charles H. Cocke  
 William de B. MacNider, Frederick R. Taylor, Charles H. Cocke  
 Thurman D. Kitchin, C. C. Carpenter, Hubert B. Haywood, Charles H. Cocke

## NORTH DAKOTA

Arthur Conwell Fortney, Fargo

Robert B. Radl, Leonard H. Fredricks, Julius O. Arnson

## OHIO

Tom Douglas Spies, Cincinnati  
 Roy Wesley Scott, Cleveland  
 Joseph Treloar Wearn, Cleveland  
 Casimir Joseph Czarnecki, Toledo

James S. McLester, Fred Wilkerson, A. B. Brower  
 V. C. Rowland, Walter M. Simpson, A. B. Brower  
 Howard T. Karsner, J. M. Hayman, Jr., A. B. Brower  
 C. W. Waggoner, Frank C. Clifford, A. B. Brower

## OKLAHOMA

John Barnhart Morey, Ada  
 Elbert Henderson Shuller, McAlester  
 Frederic Griffin Dorwart, Muskogee  
 Coyne Herbert Campbell, Oklahoma City

Hugh Jeter, J. T. Martin, Lea A. Riely  
 Henry H. Turner, L. J. Moorman, Lea A. Riely  
 E. Rankin Denny, Russell C. Pigford, Lea A. Riely  
 Henry H. Turner, L. J. Moorman, Lea A. Riely

## PENNSYLVANIA

Willard Daniel Kline, Allentown  
 Richard Thomas Ellison, Philadelphia  
 Hugh McCauley Miller, Philadelphia  
 Merritt Henry Stiles, Philadelphia  
 John Harrington Willard, Philadelphia

Henry I. Klopp, Laurence C. Milstead, Edward L. Bortz  
 H. L. Bockus, Ralph Pemberton, Edward L. Bortz  
 David Riesman, H. L. Bockus, Edward L. Bortz  
 T. Grier Miller, Charles C. Wolferth, George Morris Piersol, Edward L. Bortz  
 H. L. Bockus, H. Leon Jameson, Edward L. Bortz

*Fellowship Candidates*

Albert Preston Knight, Sayre  
 Wilfred Derwood Langley, Sayre  
 Hyman Abraham Slesinger, Windber

*Sponsors*

Stanley D. Conklin, John M. Higgins, Edward L. Bortz  
 Stanley D. Conklin, Charles H. DeWan, Edward L. Bortz  
 Horace B. Anderson, Elwood W. Stitzel, R. R. Snowden

## RHODE ISLAND

Morgan Cutts, Providence

Elihu S. Wing, Charles F. Gormly, Alex. M. Burgess

## SOUTH DAKOTA

Donald Luther Kegaries, Rapid City

Charles F. Morsman, Nelson W. Barker, John L. Calene

## TENNESSEE

Edward Guy Campbell, Memphis  
 Henry Bragg Gotten, Memphis  
 Joseph Franklin Hamilton, Memphis

Conley H. Sanford, William Calvert Chaney, J. O. Manier  
 Richard E. Ching, William Calvert Chaney, J. O. Manier  
 Conley H. Sanford, William Calvert Chaney, J. O. Manier

## TEXAS

Jesse Bedford Shelmire, Dallas  
 Leslie McKnight Smith, El Paso  
 Henry Napoleon Gemoets, Houston  
 David Robert Sacks, San Antonio

C. Frank Brown, D. W. Carter, Jr., M. D. Levy  
 Orville E. Egbert, James J. Gorman, M. D. Levy  
 Alvis E. Greer, David Greer, M. D. Levy  
 Lee Rice, Herbert Hill, M. D. Levy

## VIRGINIA

Burbridge Scott Yancey, Harrisonburg

J. Edwin Wood, Jr., H. B. Mulholland, Walter B. Martin

## WASHINGTON

Harry Joseph Friedman, Seattle  
 Edward David Hoedemaker, Seattle

Lester J. Palmer, G. A. Dowling, C. E. Watts  
 Edwin G. Bannick, George H. Anderson, C. E. Watts

## WEST VIRGINIA

Pat Alexander Tuckwiller, Charleston  
 Frank Jackson Holroyd, Princeton

Martin Loxley Bonar, Walter E. Vest, Albert H. Hoge  
 Walter E. Vest, C. A. Ray, Albert H. Hoge

## WISCONSIN

Benjamin Jaffee Birk, Milwaukee

Andrew I. Rosenberger, Oscar Lotz, Rock Sleyster

## CANAL ZONE

Gilbert Miller Stevenson, Gamboa

C. D. Briscoe, T. G. Guardia, William M. James

## TERRITORY OF HAWAII

Stewart Edward Doolittle, Honolulu  
 Richard Eugene DeMonbrun Kepner, Honolulu

Hastings Howland Walker, Nils P. Larsen, Harry L. Arnold  
 Hastings Howland Walker, A. G. Schnack, Harry L. Arnold

*Fellowship Candidates**Sponsors*

## DOMINION OF CANADA

*British Columbia*

Harold Archibald Des Brisay, Vancouver      G. F. Strong, George H. Anderson, C. E. Watts

*Nova Scotia*

John Wilfred MacIntosh, Halifax      Gerald R. Burns, R. J. Collins, H. A. Farris

*Ontario*

Trenholm Lawrence Fisher, Ottawa      Warren S. Lyman, D. Slater Lewis, J. H. Holbrook

*Resolved*, that the following list of 9 be and herewith are elected to Fellowship in the American College of Physicians as of March 31, 1940:

## CONNECTICUT

Barnett Greenhouse, New Haven      Benedict R. Harris, C. J. Bartlett, Francis G. Blake

## FLORIDA

Lucien Young Dyrenforth, Jacksonville      R. H. McGinnis, William W. Kirk, T. Z. Cason

## GEORGIA

Harold Cook Atkinson, Macon      T. E. Rogers, Stewart R. Roberts, Glenville Giddings

## MASSACHUSETTS

James Harvey Townsend, Boston      Albert A. Hornor, G. Philip Grabfield, William B. Breed

## NEW YORK

Calvus Elton Richards, Clifton Springs      Mark A. Brown, John H. Skavlem, Nelson G. Russell  
 Samuel S. Paley, New York      Barnet P. Stivelman, Charles Walter Clarke, C. F. Tenney  
 Harold Inman Gosline, Ossining      Myrtelle M. Canavan, Henry A. Christian, C. F. Tenney

## SOUTH CAROLINA

Lucius Emmett Madden, Columbia      O. B. Mayer, J. Heyward Gibbes, Kenneth M. Lynch

## VIRGINIA

Andrew DeJarnette Hart, Jr., University      J. Edwin Wood, Jr., H.B. Mulholland, Walter B. Martin

## ELECTIONS TO ASSOCIATESHIP

December 17, 1939

## ARIZONA

Leslie Rest Kobert, Phoenix      Howell Randolph, Joseph Bank, Fred G. Holmes  
 Hilton John McKeown, Phoenix      Robert S. Flinn, Orville Harry Brown, Fred G. Holmes  
 William Grant Ure, Tucson      Cyrus C. Sturgis, Arthur C. Curtis, Fred G. Holmes

## CALIFORNIA

George Berdelle Hanson, Long Beach      J. E. Walker, Fred B. Clarke, James F. Churchill

*Fellowship Candidates*

Roy Alexander Ouer, San Diego  
 Harold Chester Torbert, San Diego  
 Andrew Benton Stockton, San Francisco

*Sponsors*

William H. Barrow, Lyell C. Kinney, James F. Churchill  
 J. W. Sherrill, Arthur A. Marlow, James F. Churchill  
 Dwight L. Wilbur, Arthur L. Bloomfield, Ernest H. Falconer

## COLORADO

Clarke Horace Barnacle, Denver  
 Robert Todd Terry, Denver

Ward Darley, Jr., R. W. Arndt, James J. Waring  
 Ward Darley, Jr., C. S. Bluemel, James J. Waring

## CONNECTICUT

Edward Gipstein, New London  
 Carl Hendricks Wies, New London  
 Sidney Weinberg Jennes, Waterbury

Hugh B. Campbell, Cole B. Gibson, Charles H. Turkington  
 Arthur Bliss Dayton, George Blumer, Francis G. Blake, Charles H. Turkington  
 William E. Hill, John H. Foster, Charles H. Turkington

## DISTRICT OF COLUMBIA

Samuel Benjamin, Washington  
 Linn Fenimore Cooper, Washington  
 Harry Filmore Dowling, Washington  
 Joseph Francis Elward, Washington  
 Kenneth Francis Laughlin, Washington  
 Benjamin Manchester, Washington

J. Winthrop Peabody, William P. Argy, Wallace M. Yater  
 John Minor, Lewis C. Ecker, Wallace M. Yater  
 Walter K. Myers, Soma Weiss, Wallace M. Yater  
 Oscar B. Hunter, Isidore Lattman, Wallace M. Yater  
 Eugene R. Whitmore, Joseph L. Gilbert, Wallace M. Yater  
 Janvier W. Lindsay, E. Clarence Rice, Wallace M. Yater

## MEDICAL CORPS, U. S. NAVY

Joseph La Monte Zundell, Chelsea, Mass.

E. C. White, John M. McCants, Ross T. McIntire

## FLORIDA

Francis Dowdle Pierce, Fort Lauderdale  
 Samuel Marion Salley, Miami  
 David Wyest Exley, Miami Beach  
 Frazier James Payton, Miami Beach

Kenneth Phillips, P. B. Welch, T. Z. Cason  
 Warren W. Quillian, P. B. Welch, T. Z. Cason  
 Theodore J. Pfeffer, Frank S. Perkin, T. Z. Cason  
 William M. LeFevre, P. B. Welch, T. Z. Cason

## GEORGIA

Lawrence Easter Geeslin, Brunswick  
 John Richard Shannon Mays, Milledgeville

V. P. Sydenstricker, John B. Youmans, Glenville Giddings  
 George L. Echols, V. P. Sydenstricker, James E. Paullin, Glenville Giddings

## ILLINOIS

Richard Brooks Capps, Chicago  
 Angelo Samuel Geraci, Chicago  
 Donald Anton Hirsch, Chicago  
 Gilbert Henry Marquardt, Chicago  
 Eugene Lawrence Walsh, Chicago

J. Roscoe Miller, Laurence E. Hines, James G. Carr  
 Robert S. Berghoff, Italo F. Volini, James G. Carr  
 Robert S. Berghoff, Italo F. Volini, James G. Carr  
 J. Roscoe Miller, A. A. Goldsmith, James G. Carr  
 J. Roscoe Miller, Laurence E. Hines, James G. Carr

*Fellowship Candidates*

George Clarence Turnbull, Evanston  
 Arthur Sterling Webb, Wheaton

*Sponsors*

Samuel J. Lang, Lowell D. Snorf, James G. Carr  
 Walter H. Watterson, Josiah J. Moore, James G. Carr

## INDIANA

Thomas Olney Dorrance, Bluffton  
 Arthur B. Richter, Flora  
 Brandt Ferguson Steele, Indianapolis

Allen A. C. Nickel, Gustav L. Kaufmann, Robert M. Moore  
 Edgar F. Kiser, J. O. Ritchey, Robert M. Moore  
 J. O. Ritchey, Edgar F. Kiser, Robert M. Moore

## KANSAS

Lewis George Allen, Kansas City  
 Floyd Cornelius Taggart, Topeka

Fred E. Angle, Fred J. McEwen, Thomas T. Holt  
 William C. Menninger, Philip W. Morgan, Thomas T. Holt

## LOUISIANA

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WinnipegCharles Hutchinson A'Court Walton,  
WinnipegJohn M. McEachern, J. Currie McMillan, Fred  
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## OBITUARIES

### DR. WILLARD C. STONER

Dr. Willard C. Stoner of Cleveland, Ohio, died November 15, 1939 at 62 years of age. Dr. Stoner was educated at Ohio Northern University, Defiance College and Ohio Wesleyan University. He pursued graduate study at the University of Michigan, University of Chicago, Johns Hopkins Hospital, Harvard University, University of Berlin, University of Munich and University College Hospital, London.

In the World War, Dr. Stoner organized a medical unit and served as the medical chief of Base Hospital No. 52. He was staff consultant as well as receiving and evacuating officer at Rimacourt, France. Later he was commanding officer and chief of medical service at Evacuation Hospital No. 3, Army of Occupation, Treves, Germany. At the end of the war he held the rank of Colonel in the Medical Reserve Corps and Commanding Officer of General Hospital 246.

In the death of Dr. Stoner the medical profession of Cleveland lost one of its foremost leaders. In 1918 he was appointed Medical Director of St. Luke's Hospital and played a major rôle in developing the present institution. He visualized the modern hospital as a dominant progressive factor in educating the community in health matters as well as for actual professional training and care of the sick. He was a firm believer in the dictum of providing hospital care for the greatest number of individuals at the lowest possible cost.

Dr. Stoner lived for medicine and from it he derived his greatest joy in life. Early in his medical career, Dr. Stoner realized the importance of scientific research in connection with the practice of medicine. This was evidenced by the fact that he was the first to introduce the Wassermann test to Cleveland. He was the author of numerous publications and addresses before various medical societies. In 1937 an anonymous donor gave St. Luke's Hospital \$10,000.00 to be known as the Willard C. Stoner Fund, to be used in support of medical research and graduate medical education.

Dr. Stoner became a Fellow of the American College of Physicians in 1920 and was certified by the American Board of Internal Medicine in 1937.

In his private practice Dr. Stoner well understood the value to the patient of a serene attitude and he helped many to achieve it. His fine achievements and the blessings that his practice conferred on countless individuals in all walks of life, will remain as a consolation to his many friends and an enduring source of pride to his family.

ROBERT A. READING, M.D. (Associate)

## DR. ALLAN JOSEPH HRUBY

Allan Joseph Hruby died on November 18, 1939, of lobar pneumonia. Dr. Hruby was born in Chicago the 27th of April, 1890. He took his degree in medicine at the University of Illinois College of Medicine in 1913 and subsequently served an internship at the Cook County Hospital from 1913 to 1915. This was followed by a research fellowship at the Wesley Memorial Hospital from 1915 to 1916. He was Instructor in Didactic Medicine at the University of Illinois from 1913-1915; Health Officer, City of Chicago Health Department, 1916-1917; Head Clinic Physician, Municipal Tuberculosis Sanitarium, 1917-1918; Medical Superintendent, Municipal Tuberculosis Sanitarium, 1918-1922; Instructor in Public Health Nursing, School for Home and Public Health Nursing, 1918-1922; Secretary and Member of the Board of Directors, City of Chicago Municipal Tuberculosis Sanitarium; Member of the staff at Cook County, St. Anthony's and Washington Boulevard Hospitals; Consulting Physician, Chicago, Milwaukee, St. Paul and Pacific Railroad Co.; Member, Chicago Medical Society, Illinois Medical Society (Fellow), American Medical Association, Bohemian Medical Society, Chicago Tuberculosis Society, National Tuberculosis Association (Fellow), American Public Health Association, Diplomate of the American Board of Internal Medicine, and has been a Fellow of the American College of Physicians since December 20, 1931.

Dr. Hruby left a host of friends both among his patients and his fellow practitioners. All those who knew him regretted very much his untimely death. He was still in the prime of life and giving excellent service to his patients by whom he will be greatly missed. Dr. Hruby was a man of pleasing manner and approach, well-trained and a hard worker who had established an excellent reputation for himself not only in Chicago but throughout the country, especially among the men who were interested in tuberculosis. The profession and the community have lost a fine physician and a worthy citizen.

JAMES G. CARR, M.D., F.A.C.P.;  
Governor for Michigan

## DR. JOHN WILSON TAPPAN

John Wilson Tappan, M.D., F.A.C.P., El Paso, Texas, died September 2, 1939, at an El Paso Hospital.

Dr. Tappan was born September 12, 1867, at Ogden, Kansas. His academic education was received at the St. Mary's College, Kansas, and at the Massachusetts Institute of Technology. His medical education was begun in 1894 under a preceptor at Roan Mountain, Tenn., and later completed at the Medical Department of the University of Virginia, where he served as demonstrator in Anatomy. He was appointed Interne in the Marine Hospital Service for duty in the immigrant wards of the Long Island

College Hospital, Brooklyn; appointed Acting Assistant Surgeon in 1899, he continued on duty in the Hospital for four years, when he was detailed to Ellis Island for duty in connection with medical inspection of immigrants, until 1906, when he accepted a position as Chief Surgeon with the LaFollette Coal, Iron and Railway Co., LaFollette, Tenn. When this company was about to suspend operations, he again entered the United States Public Health Service, and was reassigned to duty at El Paso, Texas, in 1907.

In addition to this service, Dr. Tappan became quarantine officer in 1910, and during the years 1915 to 1917 he was permitted by the Public Health Service to accept the position of City Health Officer of El Paso, at the request of the mayor and city council, during a typhus epidemic. During the World War, he organized and had charge of the Venereal Clinic established by the United States Public Health Service and the American Red Cross. This clinic, afterwards known as United States Government Clinic No. 5, was established January 26, 1918, and was transferred to the city and county of El Paso, July 18, 1919.

In 1924, Dr. Tappan was made supervisor of the border between the United States and Mexico, and in 1925 had charge of the anti-yellow fever work on the Texas-Mexico border. In 1926 he was assigned to duty at the United States Marine Hospital, Fort Stanton, New Mexico, and in 1929 was assigned the position of Officer in Charge of the San Diego Quarantine Station, Port Loma, Calif. Retiring from the Public Health Service in 1933, Dr. Tappan returned to El Paso, where he became director of the City-County Health Department, resigning in 1938 because of his health. In 1939 the Texas State Medical Association conferred upon him the distinction of Honorary Member.

Dr. Tappan contributed a number of articles to medical literature on subjects in his chosen field of public health. He was a member and ex-President of the El Paso County Medical Society, member of the State Medical Association, and the American Medical Association; the Southern Medical Association, the Medical and Surgical Associations of the Southwest, the Association of Military Surgeons, and the Retired Officers Association, and had been a Fellow of the American College of Physicians since April 7, 1929. His death closed the career of a successful physician and public health executive, who was esteemed by all who knew him.

M. D. LEVY, M.D., F.A.C.P.

Governor for Texas

#### DR. CHARLES CLIFTON BROWNING

Dr. Charles Clifton Browning, F.A.C.P., San Marino, Calif., died September 28, 1939, of lobar pneumonia. He had not been in good health since a cerebral attack during October, 1932.

Dr. Browning was born at Denver, Illinois, in 1861. His family removed to Shelbyville, Mo., where young Browning attended the local high

school and later entered the Christian University at Canton, Mo. He graduated from the University of Missouri School of Medicine in 1883. Following this he returned to Denver, Ill., where he practiced for five years and then took a position as Assistant Physician at the New York City Asylum for the Insane. In 1891 he removed to California, seeking better health, and located first in San Jacinto and later in Highland.

While at the latter location he became interested in the black widow spider and made extensive studies of its habits. He supplied the Smithsonian Institution with its first specimens and his first researches on this subject were published in the Southern California Practitioner, August, 1901.

Dr. Browning became Medical Director of the Pottenger Sanatorium, Monrovia, in 1905, remaining five years, when he entered private practice in Los Angeles, his work being limited to tuberculosis. During the following twenty-two years he was an acknowledged leader, not only in his special field of medicine, but in all medical activities. He was one of the group responsible for the adoption and development of the California County Tuberculosis Sanatoria, under supervision of the California State Board of Health, which is said to be accountable for the high standard of care given patients in California public institutions. Dr. Browning, in addition to serving several terms as President of the California Tuberculosis Association, was a Director of the National Tuberculosis Association, a member of the Los Angeles County Medical Association, California State Medical Association, American Climatological and Clinical Association, the Association for the study of Internal Secretions, and many other local and State societies. He was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1920. He was the author of many articles appearing in leading medical journals.

During the World War he was one of the few men beyond the age limit who were admitted to the service, being assigned as Chief of the Medical Service at Fort MacArthur in 1918-19. From 1918, until his retirement, he was Professor of Tuberculosis in the College of Medical Evangelists and he had been, since 1910, Chief of the Attending Staff of the Tuberculosis Service at the County Hospital.

Dr. Browning took an active part in community matters. His influence as a teacher was far reaching and his students and fellow members in the profession, as well as his patients, felt the imprint of his kindly spirit and sympathetic understanding. He was esteemed by all who knew him.

Courtesy of Edward W. Hayes, M.D., F.A.C.P., and "California and Western Medicine."

#### DR. HERMAN TROSSBACH

Dr. Herman Trossbach died of chronic nephritis with hypertension at the age of fifty-eight at the Hackensack Hospital, on October 1, 1939. Dr.

Trossbach was born in Carlsbadt, N. J., where he lived until he went to Jersey City where he went to High School and then did his college work at night at Cooper Union. He was graduated from the Long Island College of Medicine in 1907 and interned at the Englewood Hospital, Englewood, N. J., 1907-1908. Following this he went with his family to Colorado Springs, Colorado, where he began the practice of medicine. About 1918 he returned to New Jersey and took up practice in Hasbrouck Heights, moving to Bogota about 1923, where he practiced until his death.

He was a quiet scholarly gentleman, not much inclined to social life, and spent most of his spare time with his family and working in his garden. He was well known for his work with dahlias and spoke over the radio on this subject. He was respected by his fellow towns-people, but took no active part in community affairs, though giving considerable time to leadership in his profession.

He was Attending Internist at the Hackensack Hospital, at one time president of its Medical Board, and at the time of his death Director of Medical Service in that institution. He was Attending Physician at the Holy Name Hospital, Teaneck, N. J.

He was a member of the Bergen County Medical Society of which he was president in 1926, the New Jersey State Medical Society, the Association for the Study of Internal Secretions, the American Medical Association, and had been a Fellow of the American College of Physicians since 1928.

In 1913 he married Miss Mine Augustin. His wife and two children survive him.

GEORGE M. KNOWLES, M.D., F.A.C.P., and  
GEORGE H. LATHROPE, M.D., F.A.C.P.,  
Governor for New Jersey

#### DR. CHARLES FALKOWSKY, JR.

It is with sincere regret that The American College of Physicians notes the passing of Dr. Charles Falkowsky, Jr., of Scranton, Pennsylvania, who had been elected to Fellowship in 1928.

Dr. Falkowsky was born in Scranton in 1880. He graduated from the Scranton Business College in 1897, and received his degree of Doctor of Medicine from the University of Pennsylvania School of Medicine in 1901. Dr. Falkowsky's internship was taken at the Kings County Hospital in Brooklyn from 1901 to 1903.

From 1906 to 1912 Dr. Falkowsky was Assistant Physician at the Scranton State Hospital. In 1912 he became Chief Physician, which position he held until the time of his death. He was also Consulting Physician at the Nanticoke State Hospital from 1926 to date. He was Physician at the Mercy Hospital from 1930 to date of death.

During the World War, Dr. Falkowsky was Captain of the Medical Corps, United States Army, and Chairman of the Medical Advisory Board.

Society affiliations include membership in the Lackawanna County Medical Society in which society he was also a former President, Member and ex-Chairman of the Medical Section of the Pennsylvania State Medical Society, Fellow, American Medical Association, Member, American Therapeutic Society, Fellow, The American College of Physicians since 1928.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania.

### DOCTOR JOSEPH EDMOND DUBÉ

Dr. Joseph Edmond Dubé, of Montreal, Professor of Clinical Medicine in the University of Montreal for the past nineteen years, died at the Hotel Dieu hospital in Montreal on November 25, 1939.

Doctor Dubé was born in Montreal on March 10, 1868.

He took his primary education at Joliette and then studied medicine at Laval University, Montreal, where he graduated in 1894. He then went to Paris for postgraduate study, receiving the State diploma in 1896.

On his return to Montreal he was appointed to the staff of the Hotel Dieu in 1897.

Very shortly after his return he took an active leading part in the medico-social activities of the Province of Quebec.

His success along these lines was due largely to his winning personality and the esteem in which he was held in this community. In 1903 Dr. Dubé took part in the founding of the two institutions for tuberculosis—The Royal Edward and the Bruchesi Institute. From that date onwards, he played a leading part in all educational work on tuberculosis in the Province of Quebec.

In addition to his work on tuberculosis he was one of the founders of the Montreal Medical Society, and the Goutte de Lait.

He was a director of the medical journal—'Union Medicale du Canada'; a member of the Royal College of Physicians and Surgeons of Canada, and a Fellow of the American College of Physicians.

Furnished through the courtesy of Charles F. Moffatt, M.D., F.A.C.P.,  
Governor for Quebec.

# ANNALS OF INTERNAL MEDICINE

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## CHEMICAL CHANGES IN THE BLOOD OF PATIENTS WITH PYLORIC OBSTRUCTION \*

By PAUL H. NOTH, M.D.,<sup>†</sup> and DWIGHT L. WILBUR, M.D., F.A.C.P.,<sup>‡</sup>  
*Rochester, Minnesota*

FOR a long time clinicians and surgeons have appreciated the fact that a close relationship exists between loss of gastric and duodenal content by vomiting or through a fistula and changes in the chemical composition of the plasma of the blood. The importance of recognizing these changes in patients suffering from pyloric obstruction in whom surgical treatment is to be carried out has been amply proved by the reduction in mortality which has followed adequate preoperative preparation of patients. While the mechanisms leading to some of the chemical changes, for example, elevation of the values for urea content of the blood, have not been clearly established, fortunately therapeutic measures such as administration of a physiologic solution of sodium chloride have proved adequate in most cases to return the urea and the serum electrolytes to normal or relatively normal levels.

In the usual cases of pyloric obstruction the characteristic changes in the composition of the blood include a decrease in the level of chlorides in the plasma, an increase in the values for urea nitrogen in the blood and an increase in the power of the blood to combine with carbon dioxide. The decrease in the plasma chlorides has been explained as a result of loss of chlorides by vomiting or through the intestine, of shift of chlorides from the blood to the tissues or of possible shift of chlorides from the plasma to the corpuscles. The mechanisms leading to an elevation of the content of nonprotein nitrogen in the blood are less clearly understood than are those resulting in decreased values for plasma chlorides. However, the following factors have been considered at various times to be of etiologic significance: (1) increased destruction of body protein due to the effect of some toxic substance or as a result of dehydration; (2) decreased function of the kid-

\* Submitted for publication August 24, 1938.

<sup>†</sup> Now residing in Detroit, Michigan.

<sup>‡</sup> Now residing in San Francisco, California.



neys resulting from dehydration or "toxic nephritis"; (3) hypochloremia resulting in elevation of the level of urea as a compensatory mechanism for maintaining the osmotic pressure of the blood; (4) alkalosis following marked vomiting or the administration of alkalis for therapeutic purposes. The increase in the bicarbonate content of the blood seems to be a compensatory process due to loss of chloride ions. Peters and Van Slyke<sup>1</sup> have pointed out that "although chloride deficiency is the most prominent feature of pyloric obstruction, dehydration and base deficiency seem to have more critical significance and are the factors which are responsible for the most of the serious symptoms and death."

The present study has been made for the purpose of evaluating if possible the significance of certain clinical factors which may be of importance in producing changes in the blood in cases of pyloric obstruction.

### MATERIAL STUDIED

The present study is based on the records of 151 patients suffering from duodenal or gastric ulcer or from gastric carcinoma complicated by pyloric obstruction, demonstrated by clinical or roentgenologic examination or by intubation of the stomach. The history of vomiting of large quantities of gastric content, usually containing retained food remnants, retention of abnormal quantities of barium during roentgenologic examination of the stomach, or the retention of over 300 c.c. of gastric content one hour after the Ewald test meal (normal 200 c.c. or less) has been considered as evidence of pyloric obstruction and gastric retention.

A certain number of patients with abnormal values in the blood have been purposely selected for study in the hope of determining the importance of clinical factors such as vomiting, the concentration of hydrochloric acid in the gastric juice and the extent of pyloric obstruction in leading to the development of chemical alterations in the blood. Consequently the material does not permit of an analysis for the frequency of occurrence of abnormal values for urea, chlorides, and carbon dioxide content in an unselected group of patients.

Table 1 indicates the sex and age incidence of the patients and the type of lesion which was present. Approximately two-thirds of the patients had pyloric obstruction as a result of a duodenal or gastric ulcer while in the remaining third carcinoma of the stomach produced the obstruction.

For all of the patients studies have been made of the values of at least one of the following: plasma chlorides expressed as sodium chloride, blood urea and carbon dioxide combining power of the blood. For many patients data have been obtained in regard to the levels of gastric acidity, the amount of retained content in the stomach, the amount of gastric content usually vomited and the duration of vomiting, as well as such factors as the percentage of hemoglobin, results of urinalysis, and roentgenologic and surgical observations. Consideration has been given also to certain additional

factors which might influence the chemical constituents of the blood, namely, renal changes due to arteriosclerotic renal or obstructing urinary lesions, and gastrointestinal hemorrhages.

Sufficient data could not be obtained to permit quantitative studies of the chloride and nitrogen metabolism of patients suffering from pyloric obstruction. It was hoped that the material studied would be sufficient to permit the evaluation in a gross way of certain of the factors which may influence chemical changes in the blood of these patients. It seemed reasonable to believe that the presence or absence of vomiting, and perhaps to some extent the amount of gastric content vomited, the duration of vomiting, the presence or absence of free hydrochloric acid and its concentration in the gastric content and the amount of retained content in the stomach might influence significantly the level of chemical substances in the blood. A corre-

TABLE I

Age and Sex of Patients and Type of Associated Lesion in 151 Cases of Pyloric Obstruction

Diagnosis	Sex	Age in years			Number of cases
		Average	Youngest	Oldest	
Carcinoma of stomach	Male	58.3	36	79	43
	Female	59.0	46	75	10
	Both sexes	58.4	36	79	53
Duodenal and gastric ulcer	Male	51.2	20	81	77
	Female	49.6	23	76	21
	Both sexes	50.9	20	81	98
Total	Both sexes	53.5	20	81	151

lation of such clinical data with the levels of the plasma chlorides, the blood urea and the carbon dioxide combining power of the blood has therefore been attempted.

The patients have been divided into two groups, the first consisting of those who did not receive any treatment prior to estimation of the levels for plasma chlorides, blood urea and carbon dioxide combining power of the blood, the second consisting of patients each of whom received one or two intravenous injections of 1 liter of physiologic solution of sodium chloride and of 10 per cent *d*-glucose before the estimations of the chemical values in the blood were made.

## RESULTS

*Plasma Chlorides.* For 133 of the patients the values for plasma chlorides estimated as sodium chloride were obtained. An attempt has been made to correlate the values for plasma chlorides in these patients with a

variety of clinical factors which it was felt might influence the level of plasma chlorides.

Factors which do not correlate: The values for hemoglobin, the specific gravity of the urine, the period over which the symptom of vomiting occurred, the volume of gastric content ordinarily vomited, the amount of retained gastric content and the concentration of free hydrochloric acid in the gastric content are factors which could not be correlated with the level of plasma chlorides. Negative results also followed attempts to correlate the plasma chloride levels with combinations of these factors such as: (1) the volume of gastric content ordinarily vomited and the free hydrochloric acid in the gastric content, (2) the duration of vomiting, the volume of gastric content usually vomited and the free hydrochloric acid in the gastric content, and (3) the degree of free hydrochloric acid in the gastric content and the amount of retained gastric content.

Factors which correlate: There is a correlation between the level of plasma chlorides and a factor which we have called the amount of vomiting, which is obtained by estimating the volume of gastric content ordinarily vomited, the frequency of vomiting and the period over which the symptom of vomiting occurred (table 2). The amount of vomiting has been graded

TABLE II

Relative Values for Plasma Chloride and Amount of Vomiting in Cases of Pyloric Obstruction

Amount of vomiting,* grade	Number of cases	Plasma chlorides				
		Lower than normal values		Values in the blood (mg. per 100 c.c.)		
		Number of cases	Per cent of cases	Mean	Lowest	Highest
0	19	4	21.1	597	520	635
1	32	9	28.1	593	510	648
2	38	17	44.7	580	460	650
3	44	26	59.1	549	370	660

\* The amount of vomiting is a factor composed by estimating the volume of gastric content ordinarily vomited, the frequency of vomiting and the period over which the symptom of vomiting occurred. (See text.)

as follows: grade 0 indicates that vomiting did not occur; grade 1 indicates vomiting of small amounts of fluid two or three times a week, usually over a short period of time; grade 2 includes vomiting of small amounts of fluid almost daily or larger amounts of fluid occasionally, usually over a short period of time; grade 3 indicates that vomiting of large quantities of gastric

content occurred several times daily over a period of a week to months. Table 2 indicates that the greater the amount of vomiting, the larger is the percentage of cases with abnormally low chloride values and the lower the mean value for plasma chlorides determined as sodium chloride.

There are exceptions to these findings. Even in a group of selected patients such as that which is reported in this paper, in 41 per cent of those in whom vomiting grade 3 was present the values for plasma chlorides were within the normal range. The occurrence of abnormal values for plasma chlorides in cases without much vomiting is considerably less frequent as evidenced by the fact that in the 19 cases in which vomiting did not occur the values for plasma chlorides were essentially normal (mean 597 mg. per 100 c.c.; lowest 520 mg. per 100 c.c.; normal 570 to 620 mg. per 100 c.c.). These values are for both the treated and untreated cases.

The influence of treatment consisting of one or two intravenous injections of 1000 c.c. of physiologic solution of sodium chloride and of 10 per cent *d*-glucose is illustrated in figure 1. This figure shows clearly how rapidly the abnormal values may approach the normal after the parenteral administration of chlorides and fluid.

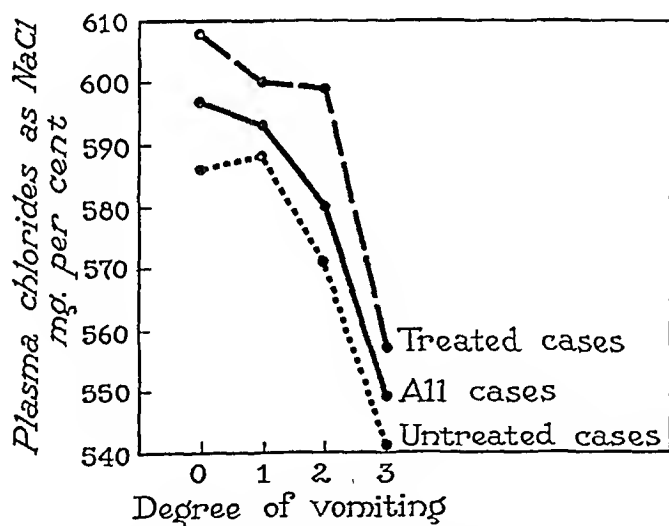


FIG. 1. Relation of plasma chlorides in blood of patients suffering from pyloric obstruction to degree of vomiting.

There is a definite correlation between the level of plasma chlorides and the carbon dioxide combining power of the blood (figure 2). The correlation of values for plasma chlorides and blood urea is discussed later in this paper.

*Blood Urea.* Factors which do not correlate: Attempts to correlate the values for the blood urea with such factors as the age of the patient, the amount of retained gastric content, the free hydrochloric acid content of the gastric juice and the carbon dioxide combining power of the blood proved

negative. Negative results also followed attempts to correlate the levels of blood urea with factors composed of multiples of any two of the following factors, namely, the amount of free hydrochloric acid in the gastric content, the amount of retained content in the stomach, the amount of vomiting and the degree of free hydrochloric acid in the gastric content.

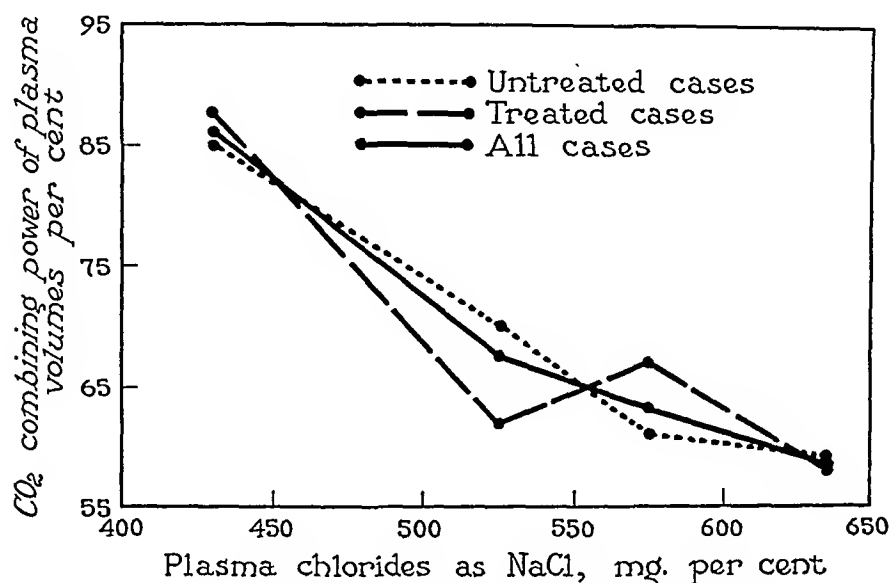


FIG. 2. Relation of the carbon dioxide combining power of the blood of patients suffering from pyloric obstruction to plasma chlorides.

Factors which correlate: We were able to establish a relation between the values for blood urea and the amount of vomiting (table 3) as was true

TABLE III

Relation of Values for Blood Urea and Amount of Vomiting in Cases of Pyloric Obstruction

Amount of vomiting, grade	Number of cases	Blood urea				
		Higher than normal values		Values in the blood (mg. per 100 c.c.)		
		Number of cases	Per cent of cases	Mean	Lowest	Highest
0	20	3	15.0	31	18	56
1	34	11	32.4	36	14	82
2	41	13	31.7	41	16	130
3	49	28	57.1	54	16	156
Total	144					

also for the plasma chlorides (table 2). The mean values for blood urea rose steadily with increases in the amount of vomiting. The values for blood urea were abnormally high in only three patients (15 per cent) of the 20 who did not vomit. That not all patients with marked vomiting have abnormal values for blood urea is indicated by the finding of normal values for urea in 43 per cent of patients with vomiting grade 3.

In general there was some correlation of the values for plasma chlorides and for blood urea as indicated by the observation that the lower the range of values for plasma chlorides the higher was the level for blood urea (table 4). In all of the 10 patients in whom the values for plasma chlorides were less than 500 mg. per 100 c.c., the values for blood urea were 40 mg. per 100 c.c. or more.

TABLE IV

Relation of the Values for Plasma Chloride to Those for Blood Urea in Cases of Pyloric Obstruction: Treated and Untreated Cases

Plasma chloride, values in mg. per 100 c.c.	Number of cases	Blood urea values in mg. per 100 c.c.		
		Mean	Highest	Lowest
500 or less	10	104.6	156	40
500-550	36	42.3	93	14
550-600	48	42.7	130	18
600 or more	57	32.9	80	14
Total	151			

*Carbon Dioxide Combining Power of the Blood.* Attempts to correlate the values for carbon dioxide combining power of the blood with many of the factors previously noted in the paragraphs on the plasma chlorides and blood urea gave essentially similar results. There was, however, definite correlation of the values for carbon dioxide combining power of the blood and the plasma chlorides as illustrated in figure 2.

*Achlorhydria.* Achlorhydria was present in 21 of the 151 patients. For most of these patients the values for gastric acidity were obtained one hour after an Ewald meal. In a few instances histamine was used as a gastric stimulant. Study of the values for plasma chlorides, blood urea and carbon dioxide combining power of the blood in patients with achlorhydria gave results essentially similar to those reported for the entire group of 151 patients.

In three of the 21 patients with achlorhydria the values for plasma chlorides were less than 580 mg. per 100 c.c. In one of these three patients vomiting did not occur, in another there was vomiting grade 2 and in the third vomiting grade 3. Four of the 17 patients with achlorhydria in whom

estimations of the values for blood urea were made had a level of urea over 50 mg. per 100 c.c. Vomiting was a prominent feature in all of these four cases (in three it was graded 3 and in one case graded 2).

*Patients with Large Amounts of Retained Gastric Content.* Analysis of the records of patients who retained a large amount of gastric content failed to reveal a greater proportion of these with abnormal chemical findings in the blood than of patients with slight retention; neither were such abnormal chemical changes more marked in patients who retained a large amount of gastric content than in patients who retained a smaller amount.

*Gastrointestinal Hemorrhage.* There were 20 patients in whom gross bleeding from the gastrointestinal tract had been of recent occurrence and in whom it was considered to be a complication in addition to pyloric obstruction. In this group of patients the mean value for blood urea was 54.5 mg. per 100 c.c. and for plasma chlorides 551.8 mg. per 100 c.c. (19 of 20 patients). This is in contrast with values for the entire group, which were as follows: for blood urea (144 patients) 40.5 mg. per 100 c.c., for plasma chlorides (133 patients) 579.75 mg. per 100 c.c.

*Patients with Hypertrophy of the Prostate Gland and Urinary Obstruction.* In 16 patients there was prostatic hypertrophy of sufficient degree to produce difficulty in urination. The mean value for blood urea in this group was 56.4 mg. per 100 c.c., for plasma chlorides 543 mg. per 100 c.c. (14 cases).

*Influence of the Type of Lesion.* There was no significant difference in the findings for the chemical changes in the blood in those patients in whom the pyloric obstruction was due to carcinoma of the stomach as compared with those in whom it was due to gastric or duodenal ulcer.

*Influence of the Intravenous Administration of Solutions of Sodium Chloride and d-Glucose.* The effect of treatment is apparent, for in those patients to whom such treatment was given the mean values for the blood urea were lower and for chlorides higher than in the group which did not receive treatment (figure 1).

## INTERPRETATION OF RESULTS

*Plasma Chlorides.* The decrease in values for plasma chlorides, which is one of the characteristic findings in the blood in many cases of pyloric obstruction, has been considered the result of loss of chlorides by vomiting or through the intestine (in patients suffering from diarrhea), of shift of chlorides from blood to tissue and of possible shift of chlorides from plasma to corpuscles in the blood.

The results obtained tend to substantiate the view that loss of chlorides by vomiting is an important and perhaps the most important factor leading to decreased values for chlorides in the plasma in cases of pyloric obstruction. In our results there was a definite relation between the amount of vomiting

and the decrease in values of plasma chlorides, for the greater the amount of vomiting the more likely was the value for plasma chlorides to be low. That loss of chlorides by vomiting is not the only factor which may influence the values for plasma chlorides in cases of pyloric obstruction is indicated by the fact that in some patients who did not vomit and in whom therefore presumably little if any loss of chlorides resulted from this source, the values for plasma chlorides were below normal, while in other patients with much vomiting and presumably loss of considerable amounts of chlorides, the values for chlorides in the plasma were essentially normal. It is possible, however, that a state of chloride deficiency may exist in some of these patients despite the normal values for plasma chlorides. A clear-cut relation could not be established between the amount of free hydrochloric acid in the gastric content and the level of plasma chlorides. One might anticipate that in patients with a high concentration of hydrochloric acid in the gastric juice and a large amount of vomiting and therefore presumably a greater loss of chlorides one would find greater changes in the values of plasma chlorides than in patients with a low concentration of hydrochloric acid in the gastric content. This, however, did not prove true. In fact in patients with achlorhydria, in whom one might anticipate loss of less chloride than in patients with free hydrochloric acid, the values for plasma chlorides were commensurate with those of the whole group. Studies of the neutral chlorides and total chlorides in the gastric juice were not made.

Other factors which may compensate for loss of chloride in these patients and explain the variable results include shift of chlorides from tissues to the blood or from corpuscles to plasma, changes in renal function leading to decreased output of chlorides in the urine, concentration of the plasma, and, lastly, variations in the intake of chlorides in the food and drink. Similarly, failure of or alterations in these compensatory mechanisms may lead to unexpected variations in the level of plasma chlorides. We have no data to indicate the importance of these various factors in this group of patients. Such information will have to come from quantitative data of the metabolism and balance of chlorides in patients suffering from pyloric obstruction.

The rather close correlation which exists between the levels of plasma chlorides and carbon dioxide combining power of the blood (figure 2) is easily understood, for as chloride ions are lost from or decrease in the plasma they are replaced in large part by bicarbonate ions. If the loss of chloride is continued or is marked, alkalosis may develop and eventually result in "gastric" tetany.

*Blood Urea.* The changes in the values for blood urea which are frequently found in patients suffering from pyloric obstruction have been explained as a result of the action of a toxic substance, of increased destruction of body proteins due to dehydration, of decreased function of the kidneys due to dehydration or "toxic nephritis," or of hypochloremia or alkalosis.

The results obtained in this study do not indicate which of these mechanisms is the most important. There is a definite relation between the amount



of vomiting and the values for blood urea. The greater the amount of vomiting, the more likely are the levels for blood urea to be elevated. This may be the result of the greater dehydration in these patients but the evidence is not conclusive. To some extent there is a correlation between the rise of blood urea and the drop of plasma chlorides but in a general way only, and the rise of urea cannot be considered a compensatory process to maintain osmotic relationships. Attempts to correlate elevation of values for blood urea with a variety of other factors previously mentioned proved unsuccessful.

Studies of the metabolism of nitrogen and urea in patients suffering from pyloric obstruction will be necessary before it will be possible to elucidate the rôle of the various mechanisms which may result in elevated values for blood urea.

Studies of the rôle which disturbed function of the kidneys may play in cases of pyloric obstruction were not complete. Examination of the urine in some of these cases reveals a high specific gravity, suggesting that the kidney function is unimpaired and that if changes of the blood occur they are the result of dehydration or other "pre-renal" factors which interfere with renal function. Previously reported<sup>2</sup> pathologic studies of the kidneys in cases of this type reveal as the outstanding abnormality degenerative changes of the tubules. The glomeruli generally appear essentially normal, and in this respect the kidneys are quite distinct from those obtained from cases of chronic glomerular nephritis, in which glomerular changes are outstanding. In the latter the retention of urea in the blood is thought to be due to the renal lesion.

It has generally been recognized that following a gastrointestinal hemorrhage there may be elevation of the values for urea in the blood. This rise has been thought to be due principally to dehydration. In our patients in whom gastrointestinal hemorrhages occurred in addition to pyloric obstruction, the mean values for blood urea were higher than in the group of patients without bleeding but no evidence has been obtained to explain this finding.

The effects of treatment on the chemical changes of the blood in pyloric obstruction are of particular interest. To some of the patients one or two intravenous injections of 1000 c.c. of physiologic solution of sodium chloride and 10 per cent of *d*-glucose were administered before estimations were made of the chemical constituents of the blood. In patients with slight changes of the blood one or two such injections were usually sufficient to restore the blood urea or plasma chlorides to normal levels, while, as might be anticipated, in patients in whom vomiting was large in amount and the changes in the blood marked, one or two intravenous injections had very little effect on the values of plasma chloride, blood urea and carbon dioxide combining power.

## CLINICAL VALUE OF THE RESULTS

From the practical standpoint the results of this study are of considerable interest. It is well recognized that patients suffering from pyloric obstruction frequently present abnormalities of the chemical composition of the blood and that these abnormalities can be readily overcome by treatment, which must be instituted preoperatively if operation is to be carried out with the minimal risk to the patient. Under what circumstances do these abnormalities of the chemical composition of the blood occur and what is to lead the physician to suspect their presence? The results of this study suggest that patients who vomit large amounts of gastric content frequently and over a considerable period of time are the ones most likely to show elevated values for blood urea and carbon dioxide combining power of the blood and decreased values for plasma chlorides. However, these changes may be found in the absence of vomiting, although this is unlikely.

According to the results of this study the type of lesion producing the obstruction, namely carcinoma of the stomach or gastric or duodenal ulcer, is not a significant factor nor is the presence or absence of free hydrochloric acid in the gastric content significant. The patients we have studied in whom achlorhydria was found presented changes essentially the same as did those patients in whom acid was present in the gastric juice. Similarly there was no significant difference in the values in the blood as between those patients who had a low concentration of free hydrochloric acid in the gastric juice and those patients in whom a high concentration of free hydrochloric acid was found.

It is probable that the alterations in the blood will be greater than those usually observed if in addition to pyloric obstruction there is gastrointestinal bleeding or hypertrophy of the prostate with urinary obstruction.

Physicians frequently wonder what studies of the blood chemistry should be made in cases of pyloric obstruction. Our results indicate that changes in the plasma chlorides and blood urea do not parallel one another except when the changes are marked—that is, if the value for plasma chloride is lower than 500 mg. per 100 c.c., the blood urea probably will be elevated, while if the chloride is 600 mg. per 100 c.c. or more the urea value probably will be within normal limits. Little advantage is to be gained by estimating the carbon dioxide combining power of the blood if the plasma chlorides are estimated, because the changes in the values of these two substances are in inverse ratio to one another.

In considering the advisability of the preoperative intravenous administration of fluids to patients suffering from pyloric obstruction it is wise not to be guided entirely by the values for various chemical factors in the blood, since dehydration and perhaps a deficiency of chlorides in the tissues may exist even in the presence of normal values in the blood.

Finally in treating the patient the physician can expect a rapid return of the abnormal values to normal levels if he administers sodium chloride,

*d*-glucose and fluid intravenously. The amount of these substances and fluid which must be given and the rapidity with which they can bring a return to normal values are roughly proportional to the degree of elevation of blood urea and the depression of the value for plasma chlorides.

### SUMMARY

A study has been made of the records of 151 patients suffering from gastric or duodenal ulcer or carcinoma of the stomach complicated by pyloric obstruction to determine the effect of certain factors which might account for the chemical alterations which occur in the blood of many such patients.

There is a positive correlation between the amount of vomiting and the decreased values for plasma chlorides, the increased values for blood urea, and the increased carbon dioxide combining power of the blood. We are unable to establish a definite relation between the values for these three chemical factors and the type of lesion present, the age of the patient, the amount of retained gastric content, the concentration of free hydrochloric acid in the gastric content, or combinations of several of these factors. The decreased values for plasma chlorides appear to be due in large part to loss of chloride as a result of vomiting but this is probably not the only factor involved.

Patients with achlorhydria as a rule show changes in the blood similar to those in patients suffering from pyloric obstruction in whom free hydrochloric acid is present in the gastric content. In patients in whom hemorrhage into the gastrointestinal tract occurs in association with pyloric obstruction the mean values for blood urea are greater than in the entire group while values for plasma chlorides are lower in these patients with bleeding than in those in whom bleeding does not occur.

Quantitative studies of the metabolism of sodium, chloride, nitrogen and bicarbonates as well as other factors will be required before it can be ascertained which of the various factors mentioned are responsible for the characteristic changes in the chemistry of the blood in cases of pyloric obstruction.

It is clearly established that the characteristic changes of the blood in patients suffering from pyloric obstruction are readily amenable in most cases to intravenous injections of physiologic solution of sodium chloride and of 5 or 10 per cent of *d*-glucose.

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# THE INFLUENCE OF INTRAVENOUS GLUCOSE INJECTIONS ON ABNORMAL ERYTHROCYTE SEDIMENTATION SPEED IN RELATION TO ACTIVITY OF INFECTION \*

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SEVERAL factors are known to influence erythrocyte sedimentation rate. Most important among these are plasma fibrinogen and globulins. Variations in sedimentation rate have been correlated with changes in the plasma proteins.<sup>1-7</sup> The liver plays a rôle in the regeneration of plasma proteins<sup>8, 9, 10</sup> and this function is impaired by infection.<sup>11-14</sup> An underlying hepatitis was empirically assumed by Gram<sup>15</sup> to be responsible for abnormal rates under all conditions. The rôle of the liver as one of the factors influencing erythrocyte sedimentation was also suggested by Snapper.<sup>16</sup> In frank liver disease, however, consistent changes in sedimentation rate have not been observed.<sup>17, 18</sup> It appears that a possible relation between abnormal sedimentation speed of erythrocytes and altered liver function has not been investigated adequately so that it is impossible as yet to formulate a definite conclusion.

After fever and leukocytosis have subsided in patients with rheumatic fever and pulmonary tuberculosis, the rapid sedimentation rate has been regarded as the main criterion of continued clinical activity of the infectious process. On this basis alone further physical inactivity is prescribed. Whereas ordinarily the abnormal rate definitely indicates active disease, in an occasional case the persistently rapid rate may possibly be independent of activity of the original disease and actually depend on a secondary disturbance, possibly in liver function, with a resulting lag in the restoration of factors responsible for the normal rate of sedimentation.

With this in mind the influence of intravenous glucose was tested in subjects with unquestionable evidence of fully active infection and in those in whom abnormal sedimentation speed of erythrocytes persisted as the main clinical criterion of activity. The beneficial influence of glucose on liver damage is well established.

## PROCEDURE

Two or three control determinations of the sedimentation rate were made by the Linzenmeier<sup>19</sup> or Cutler<sup>20</sup> methods. After the rate had become stabilized with minimal variations, glucose injections were begun. Twenty to 50 c.c. of 25 or 50 per cent glucose were administered intravenously, daily, for four or six days. On the alternate days, 24 hours after each injection,

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the sedimentation rate was determined. After the total number of injections had been completed, the rates were determined at two or three day intervals. Determinations were made in the forenoon following a light breakfast.

## RESULTS

Glucose produced no change in the increased sedimentation rates of two patients with suppurative bronchiectasis, one with Hodgkin's disease, and one with multiple myeloma (table 1).

TABLE I

The Effect of Intravenous Glucose on Erythrocyte Sedimentation Speed in Fully Active Disease and Infection. Multiple Myeloma; Hodgkin's Disease; Suppurative Bronchiectasis

Case No.	Diagnosis	Control (Before Injection) Days			Intravenous Glucose † Days			After Glucose Days		Clinical Notes
		6	4	2	2	4	6	3	6	
F. N. 1	Multiple myeloma	7*	12	8	5	12	10	15	10	Febrile severe anemia.
T. M. 2	Hodgkin's disease	11	15	—	12	15	17	15	15	Intermittent fever. Pulmonary lesion. Leukocytosis.
G. M. 3	A putrid lung abscess, Bron- chiectasis	21	35	31	33	31	30	—	31	Low grade fever. Pus by broncho- scopy.
R. G. 4	Suppurative bronchiectasis	14	23	19	22	—	18	15	20	Subfebrile. Pus by bronchoscopy.

\* Linzenmeier method: S.R. expressed in minutes (normal rate, 18 millimeters in 60-120 minutes).

† 20 c.c. of 50 per cent glucose.

Seven patients with rheumatic fever received intravenous glucose. In cases 5, 6, and 7, with fully active carditis, fever, leukocytosis and electrocardiographic changes, glucose exercised no influence upon the abnormal sedimentation rate (table 2).

In case 8 (figure 1) glucose did not affect the rate in two series of injections during two cycles of active rheumatic infection.

Glucose exercised a definite effect on sedimentation rate in two cases (9 and 10) of subacute rheumatic fever (figures 2, 3). In case 9, the rate was slowed from a sedimentation speed of 18 millimeters in 17 minutes to 18 millimeters in 35 minutes after two injections of glucose. This rate was maintained during the injections. It continued to slow, requiring 51 minutes to sediment 18 millimeters after discontinuation of the glucose injections. In case 10, the rate slowed from a sedimentation speed of 18 millimeters in 18 and 14 minutes, respectively, to 35 minutes after three injections.

TABLE II  
Glucose Effect in Acute Rheumatic Carditis

Case No.	Diagnosis	Control (Before Injection) Days			Intravenous Glucose † Days			After Glucose Days			Clinical Notes
		6	4	2	2	4	6	2	4	6	
J. W. 5	Carditis Polyarthritidis	—	—	30*	21	29	34	53	60+	60+	No leukocytosis. E.C.G.: P-R changes. Fever (101° F.).
I. P. 6	Carditis Arthritis	14	18	21	18	22	—	30	50	59	Leukocytosis (15,400 W.B.C.). Fever (102.8° F.).
L. B. 7	Carditis Polyarthritidis	25	22	40	39	49	—	49	60+	60+	No fever or leukocytosis. E.C.G.: P-R changes.
H. B. 8	Carditis Erythema multiforme	24	21	20	20	24	—	32	44	36	See figure 1.

\* Linzenmeier method: S.R. expressed in minutes.

† 25 c.c. of 25 per cent glucose.

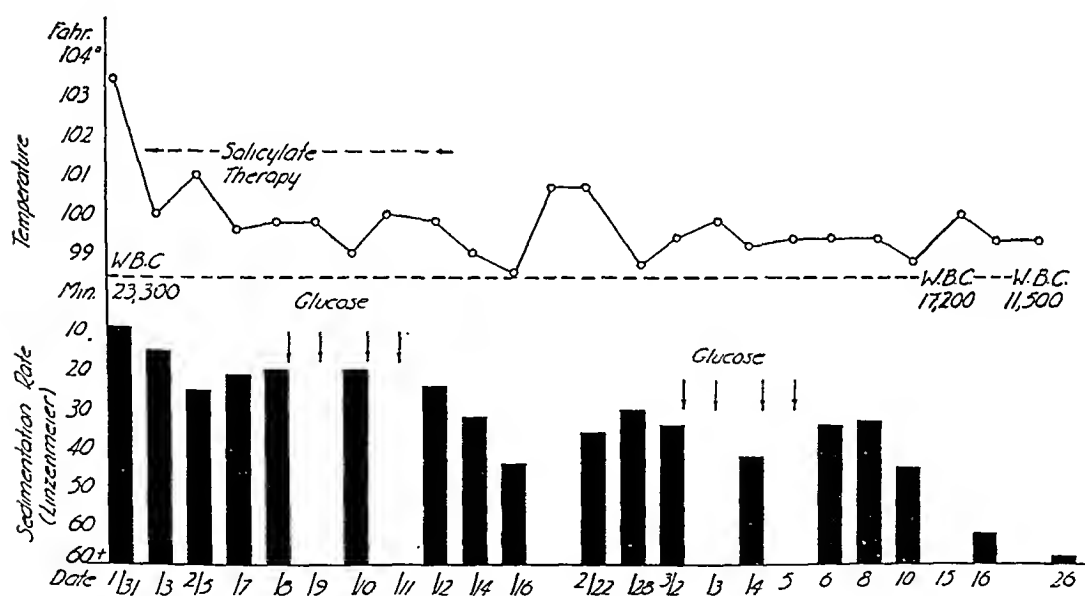


FIG. 1. (Case 8.) Acute rheumatic carditis. Erythema multiforme. Aged 13 years. Intravenous glucose without effect on sedimentation speed. Two courses of injections; 25 c.c. of 25 per cent glucose daily.

tions of glucose. This decreased sedimentation speed was maintained during the glucose period. Immediately thereafter, however, it returned to the more rapid pre-injection sedimentation speed of 18 millimeters in 18 minutes.

In the latter case the glucose produced a temporary effect, in the former a lasting effect.

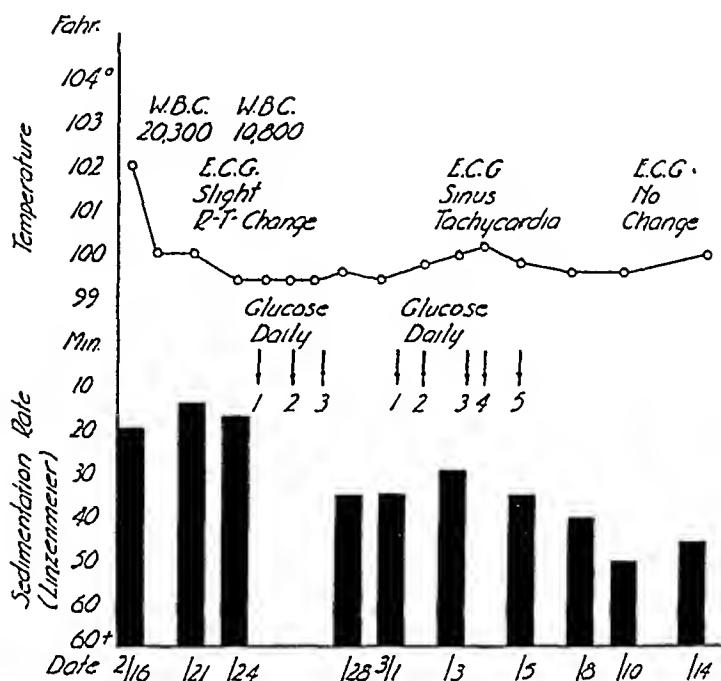


FIG. 2. (Case 9.) Subacute rheumatic carditis. Aged 14 years. Progressive slowing of sedimentation speed following both courses of intravenous glucose; 25 c.c. of 25 per cent glucose daily.

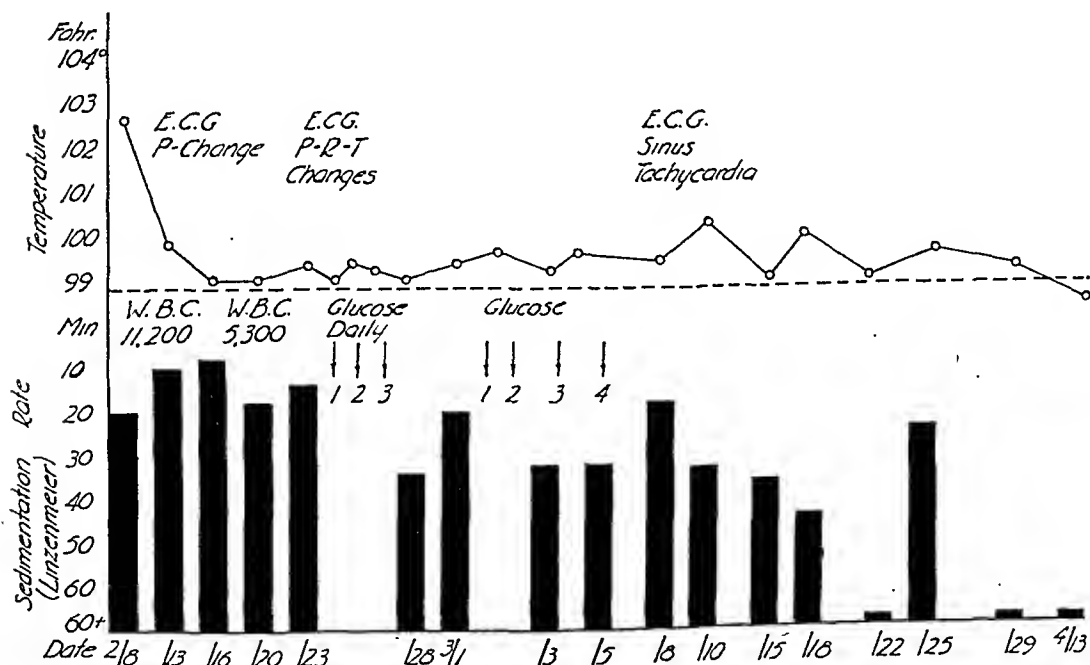


FIG. 3. (Case 10.) Subacute rheumatic carditis. Bronchopneumonia. Aged 14 years. Temporary slowing of sedimentation speed during intravenous glucose. Return to original rate after both courses of injection; 25 c.c. of 25 per cent glucose daily.

Nine patients with pulmonary tuberculosis received intravenous glucose (table 3). In three cases (cases 11, 12, 13) with fully active, febrile, moderately or far advanced tuberculosis of the lungs, glucose effected no change in the erythrocyte sedimentation rate. In two patients (cases 16, 17) with moderately advanced pulmonary tuberculosis, rated clinically inactive except for rapid sedimentation rates, glucose produced negligible changes in rate.

In the remaining four cases of afebrile, clinically inactive, moderately advanced tuberculosis definite effects were produced by glucose. In case 14 (table 3) there was a temporary retardation of the sedimentation speed of 20 and 22 millimeters in 60 minutes to 18 and 16 millimeters during the

TABLE III

Influence of Intravenous Glucose on Abnormal Sedimentation Rate in Patients with Fully Active and Clinically Inactive Pulmonary Tuberculosis \*

Case No.	Control (Before Injection) Weeks		Intravenous Glucose § Days		After Glucose Days		Clinical Notes
	2	1	3	6	3	6	
J. L. 11	22†	22	22	22	22	—	Far advanced. Fever. Pulse rapid. Cavitation. Gaffky 6.
L. K. 12	28	29	27	26	27	—	Far advanced. Fever. Gaffky 7. Cavitation.
S. S. 13	32†	25	28	30	29	—	Moderately advanced. Fever. Cavitation. Sputum negative. Artificial pneumothorax.
A. W. 14	20	22	18	16	20	20	Moderately advanced. Afebrile. No leukocytosis. Sputum negative.
M. B. 15	19	19	15	14	14	16	Moderately advanced. Small cavity. Afebrile. Pulse normal. Sputum negative.
E. de F. 16	24	23	25	22	22	24	Moderately advanced. Marked hypertension. Pulse and temperature normal. Sputum positive.
W. H. 17	20	21	20	18	—	—	Moderately advanced. Pulse and temperature normal. Sputum negative.

\* Studies made on patients with pulmonary tuberculosis were made possible through the kind cooperation of Dr. Fred. Heise, Medical Director, and Dr. John Steidl, Resident Physician, The Trudeau Sanatorium, Trudeau, New York. Dr. Lee Lichtman, Summer Intern, made the injections and the determinations in these cases.

† Cutler method: sedimentation rate expressed in millimeters (normal 6-10 mm. in 60 minutes).

‡ Linzenmeier method: sedimentation rate expressed in minutes. Case 13 only.

§ 20 c.c. of 25 per cent glucose, daily.



period of glucose injections and a prompt return to a speed of 20 millimeters in 60 minutes after the glucose. In case 15 (table 3) the rate of 19 millimeters was slowed to 14 millimeters and remained at that rate after the glucose was discontinued. In case 19 (figure 5) normal sedimentation speed was restored during the glucose phase, but the original abnormal rate was resumed immediately afterwards. In case 18 (figure 4) the normal rate which had been restored by glucose from a rapid sedimentation speed of 20 millimeters in 60 minutes persisted after glucose. The abnormal rate had existed for several months prior to the glucose test.

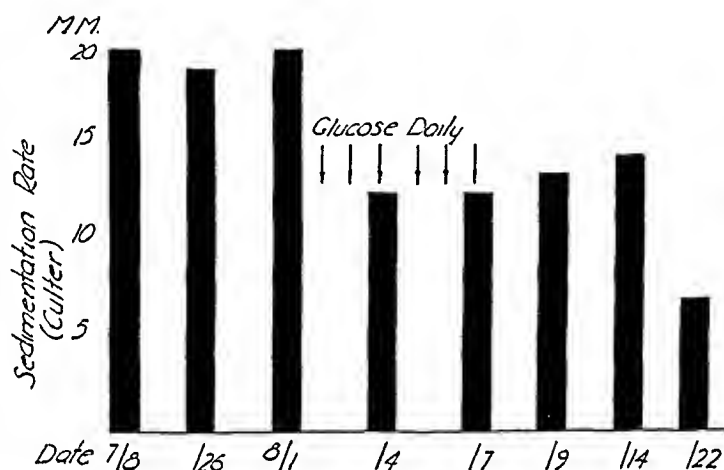


FIG. 4. (Case 18.) Moderately advanced pulmonary tuberculosis, pulse rate normal. Afebrile. Sputum positive. No cavitation. Complete restoration of normal sedimentation speed of erythrocytes during and after glucose administration; 20 c.c. of 25 per cent glucose daily.



FIG. 5. (Case 19.) Moderately advanced pulmonary tuberculosis. Pulse rate normal. Afebrile. Sputum negative. No cavitation. Temporary restoration of normal sedimentation speed during glucose administration; 20 c.c. of 25 per cent glucose daily.

## COMMENT

The slowing of the erythrocyte sedimentation speed noted in some instances after the intravenous injection of single daily doses of glucose cannot be attributed to the direct action of the sugar upon the circulating blood, since the readings were made 24 or more hours after the injection. On the contrary, the direct addition of glucose to an erythrocyte suspension has been demonstrated to accelerate sedimentation.<sup>21</sup> It is also improbable that the injected glucose directly affected the focus of infection itself histologically or immunologically. It is believed that the retarding influence of the intravenous injection of glucose on the rapid sedimentation speed of erythrocytes in some instances may depend upon the beneficial effect of glucose upon liver function in its relation to plasma protein regeneration but no direct evidence is presented to prove this hypothesis.

Liver function disturbances have been noted in rheumatic fever and in pulmonary tuberculosis.<sup>22, 23</sup> It is uncommon to find a normal sedimentation speed in active pulmonary tuberculosis whereas it is not uncommon to find a normal sedimentation rate in active rheumatic fever. It cannot be stated at present whether this latter unexpected finding can be explained on the basis of undisturbed liver function.

The converse may also be true. The persistence of a rapid sedimentation rate after the apparent subsidence of an infection, as in pharyngitis, tonsillitis, etc.<sup>24</sup> does not necessarily signify, as has been stressed, that the focus of infection is still active. There may be a lag in the restoration of the factors responsible for normal sedimentation rate after the original focus of infection has subsided.

In seven of 19 cases with abnormal sedimentation rates intravenous glucose injections definitely influenced the speed in the direction of slowing. In no case did the glucose produce a slower rate during the injection period if the abnormal rate was accompanied by fever or leukocytosis during that period. The retardation of the sedimentation speed occurring during glucose injections was usually temporary, the original sedimentation rate reverting after the injections. In one instance, in a case of moderately advanced tuberculosis (case 18) without fever and leukocytosis for several months, a normal sedimentation speed was promptly restored during the glucose injections and persisted afterwards.

On the basis of the remarkable effect of intravenous glucose on repair of liver damage, it is suggested that the slowing of the sedimentation rate, after its injection in certain patients with infections and abnormal sedimentation speeds, may possibly occur through improvement of liver function. It is fully recognized that sedimentation speed of erythrocytes is influenced by numerous other factors, known and unknown. It is suggested, however, that hepatic injury through infection may be a special factor in certain instances where abnormal sedimentation speed persists after other clinical criteria of infection indicate inactivity of infection. Under these circum-

stances intravenous glucose injections may serve promptly to restore normal sedimentation rates.

### SUMMARY

Daily intravenous glucose injections administered to 19 subjects with various types of disease and infections, including rheumatic fever and pulmonary tuberculosis, marked by abnormal erythrocyte sedimentation speed, *slowed* the sedimentation rate in seven during the period of glucose injections. *The slowing effect of the glucose was not noted if fever or leukocytosis accompanied the abnormal sedimentation speed during the period of glucose injections.*

Among numerous other factors influencing sedimentation rate, liver damage through infection and disease may in some instances influence the sedimentation speed of erythrocytes. It is suggested that intravenous glucose may serve to correct such factors although no direct evidence in support of this hypothesis is as yet available.

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# ARSPHENAMINE POISONING WITH REPORT OF FOUR CASES \*

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PREVIOUS reports concerning the toxicity of arsphenamine have described effects ranging in severity from local skin reactions to sudden death. In a recent contribution by Globus and Ginsburg, the literature has been very ably reviewed. They advance their theory as to the pathological process for which they propose a new name, "pericapillary encephalorrhagia." The pathogenesis of this process has received much consideration from others, notably Oliver and his co-workers, whose description of experimental lesions is the basis of our observations.

Joseph and Fleig showed that acid arsphenamine produced reactions due to intervacular precipitation which did not occur with alkaline disodium arsphenamine. Hanzlik and Karsner first demonstrated the agglutinating action of arsphenamine on the red blood cells. Oliver and Yamada described the early and the late toxic reaction of arsphenamine. The early reactions were due to agglutination of red blood cells resulting in embolism with the clumped cells. Late effects, such as nephritis and atrophy of the liver, do not occur as the result of embolism with agglutinated cells but are due to the chemical toxicity of the constituents of arsphenamine.

In the administration of arsphenamine, agglutination is prevented by the addition of some colloid such as gelatin, gum acacia, egg albumin and protein from blood plasma. These substances influence the action of arsphenamine on the red blood cells by preventing its absorption, with resulting agglutination and embolism. Oliver later demonstrated that this protection is due to the union of the arsphenamine with the colloids and not with the red blood cells. He further found that if the dose is greatly increased, thereby saturating the blood plasma, the excess of arsphenamine is then present in the red blood cells and agglutination and embolism occur.

## CASE REPORTS

*Case 1.* M. P., a white woman, aged 24, housewife, Italian, had been treated in the hospital dispensary during June 1931. The family history was negative, as was the history of previous illnesses. Menstrual periods had been regular without pain. The husband had been treated for syphilis 11 years before for a period of only two weeks. The patient did not know she had syphilis until a Wassermann test was made in the clinic. She had been married 11 years. She had been four times pregnant, but there was some discrepancy in the obstetrical history for it was said she had one living child and two miscarriages.

On June 28, the patient visited the clinic and received her second intravenous injection of arsphenamine. She did not feel well following this and had rather vague

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pains. On June 30, the patient was visited by her sister until about 3 p.m. and at that time she had only a few vague complaints. Her husband arrived home about five o'clock and found her sitting in a chair looking into space. She was unable to talk or to move her legs although she could move her arms. There was a tendency toward flexion at this time. She was seen by her doctor and later was admitted to the hospital on the service of Dr. Warren.

When examined she did not appear to be acutely ill, although she did not talk and was unable to cooperate. Her eyes were wide open, but she apparently was not aware of her surroundings. Her face was flushed and expressionless. There was neither nausea nor vomiting and she did not appear to have headache. Temperature was 101° F., pulse 120, respiration 22, systolic blood pressure 120, diastolic 90. The head showed no signs of trauma. The eyes reacted to light; there was a coarse nystagmus to the right and internal strabismus of the left eye. Corneal reflexes were present. The lips were very dry, and the patient resisted oral examination. The neck was not rigid and exhibited no unusual glands. The lungs and heart were normal. The arms were spastic, the fingers flexed but could be extended. The reflexes were equal and there was no evidence of paresis or paralysis. The legs were flaccid but not paralyzed, and the reflexes were normal.

Laboratory findings: red blood cells 4,250,000, white blood cells 8,400, hemoglobin 82 per cent, polymorphonuclear neutrophils 76 per cent, eosinophils 2 per cent, small lymphocytes 24 per cent, and large lymphocytes 4 per cent. The blood Wassermann test was equivocal. Cerebrospinal fluid obtained by a cisternal puncture contained 360 cells per cu. mm., polymorphonuclear neutrophils 50 per cent, large lymphocytes 50 per cent. The fluid contained globulin. Urinary examination was negative. The blood sugar was 135 mg. per 100 c.c., chlorides 644 mg. per 100 c.c., creatine 1.5 mg. per 100 c.c.

While under observation the coma seemed to deepen, the respirations became more rapid and shallow, and there was cyanosis of the lips. The pupils were contracted and there was lateral nystagmus more to the left. When stimulated the arms flexed with a fine clonic form of contraction. The skin was flushed and perspiration was very free. Pregnancy was revealed by fetal heart sounds. The temperature continued to run a septic course until on August 3 it went up to 106° F., and the patient died.

*Necropsy: Gross Findings:* The brain before fixation was extremely soft. The convolutions were flattened and the sulci narrowed. The pial blood vessels over the cortex and at the base were markedly congested, but there was no evidence of hemorrhage. The corpus collosum was ruptured due to handling, and there could be seen a large discolored area below. Examination of the brain after fixation in 10 per cent formalin did not show any gross abnormalities. On sectioning the gray matter was easily distinguished from the white matter. The discoloration appeared to be confined to the white matter extending from the mid-frontal region anteriorly to the tip of the occipital lobe posteriorly, including the basal ganglia, pons, and the cerebellum (figure 1). There was no involvement of the medulla. The ventricles did not show any undue dilatation.

*Microscopic Examination:* Sections were taken from various parts of the brain, including the discolored area, and a number of stains were made including hematoxylin-eosin, toluidine blue, Weigert-Pal, Bielschowsky, Giemsa and the Hortega-Globus modification. With the low power the pia was markedly thickened, with an infiltration of cells in the meshes of the pia, and a few blood vessels showed perivascular infiltration. With the high power the infiltrating cells were seen to be lymphocytes. The blood vessels were congested, their walls were slightly thickened and there was a perivascular infiltration of lymphocytes. In the gray matter of the cerebral cortex the ganglion cells were in a good state of preservation. There was a

moderate degree of gliosis, mostly of astrocytes and oligodendroglia (figure 6). The blood vessels in the gray matter were slightly thickened and a few showed perivascular infiltration of lymphocytes. There were no areas of hemorrhage seen in the gray matter. In the white matter, particularly in the discolored area, there were numerous ring-like hemorrhages, which varied in size and number, but were present

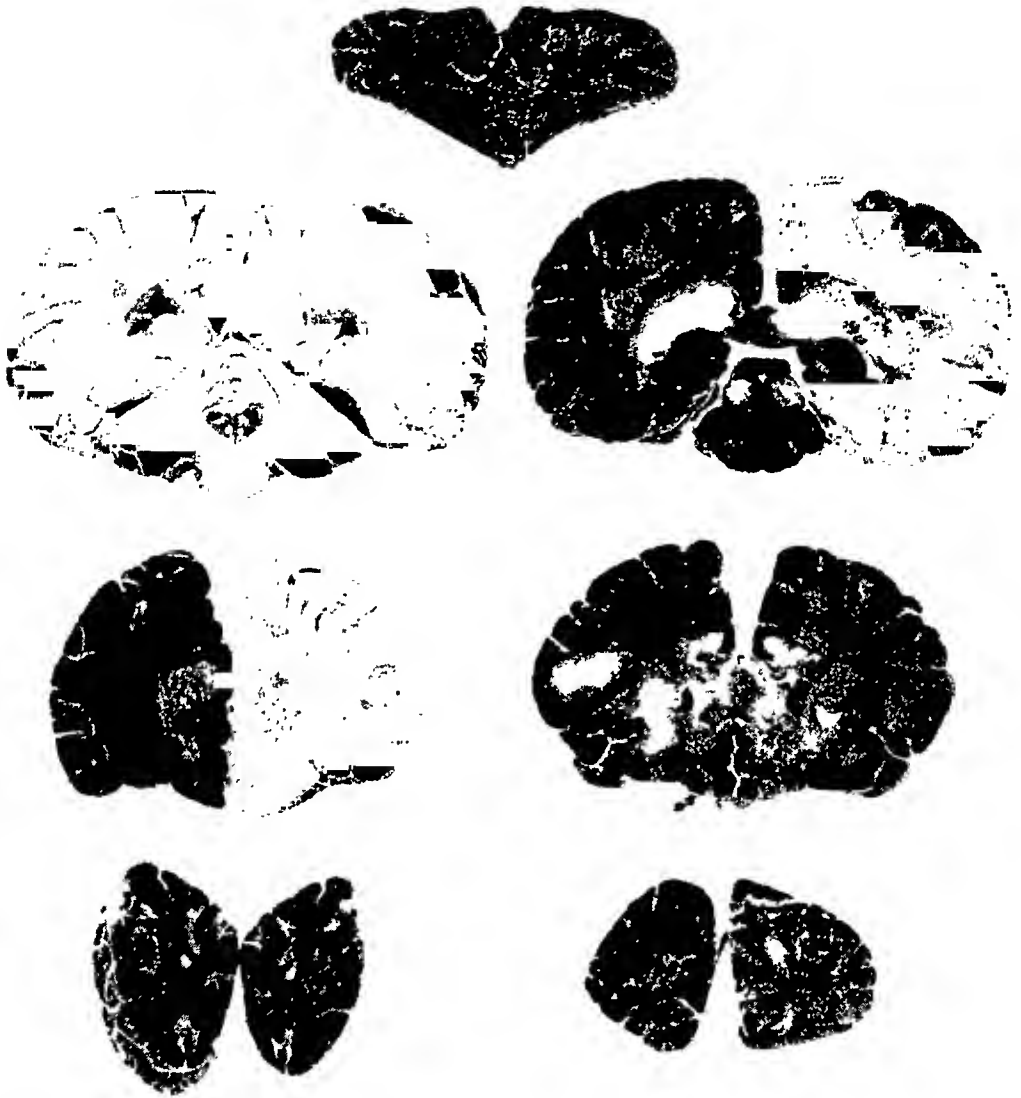


FIG. 1. The gross appearance of hemorrhages, extending from the mid-frontal region to the mid-occipital region and including the pons and cerebellum.

in all sections (figures 2 and 3). In some of these ring-like hemorrhages a central blood vessel could be seen, which in some cases was ruptured (figure 5). Around the blood vessel could be seen an area of demyelination around which was a dense ring of extravascular blood. About the latter there was a gliosis, mostly astrocytes and oligodendroglia, which extended into the tissue. In all sections from areas where this discoloration was seen in the white matter these characteristic ring-like hemor-

rhages were observed. In brief, the lesions described here are extravascular hemorrhage with rupture of the blood vessel wall, and moderate gliosis of astrocytes and oligodendroglia.

*Case 2.* A. M., a white man, aged 41, was admitted to the Kings County Hospital on January 22, 1934. He was comatose, but made aimless movements with his arms. His skin was moist and his breathing was labored. About every 15 to 20 minutes he would cry out and there would begin a series of clonic convulsive move-

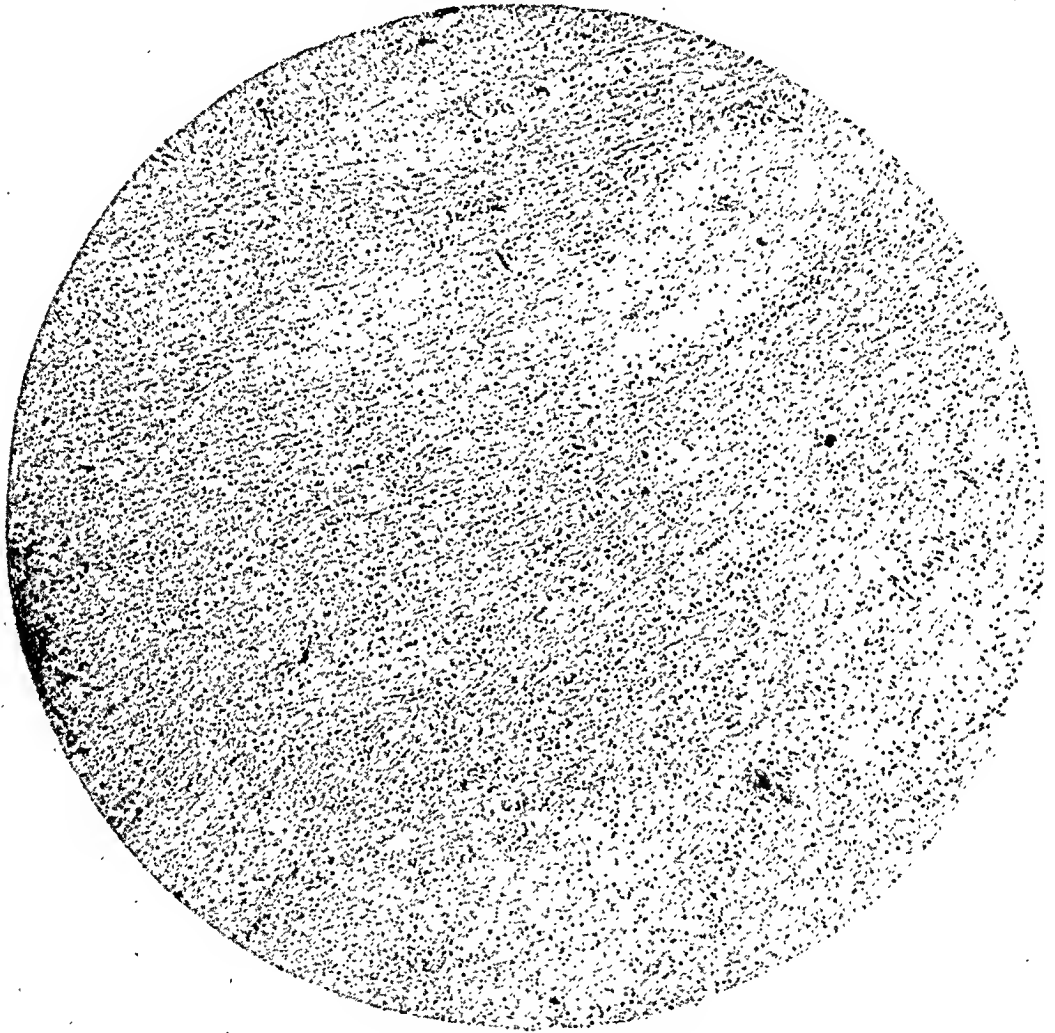


FIG. 2. Microscopic appearance under low power showing light areas around thrombosed blood vessels. Hematoxylin-eosin  $\times 70$ .

ments of both arms and legs which seemed to have the same amplitude and force on one side of the body as on the other. The head would turn to the right and there was conjugate deviation of the eyes to the right. The pupils were contracted, but there was a slight reaction to light of the right pupil, none of the left. The conjunctivae were injected. All the deep reflexes were hyperactive but equal. There was a bilateral Babinski reaction, but no ankle clonus. These convulsive seizures would last for a few minutes and then the patient would relax.



A spinal tap yielded blood tinged spinal fluid with a pressure of 22 mm. of mercury. It contained globulin (+++) and gave a paretic colloidal gold curve. Both blood and spinal fluid Wassermann reactions were strongly positive. The patient died eight and a half hours after admission to the Hospital. During this time his temperature ranged from 98.4° F. to 100° F., and his pulse from 100 to 120. Systolic blood pressure was 130, diastolic 80.

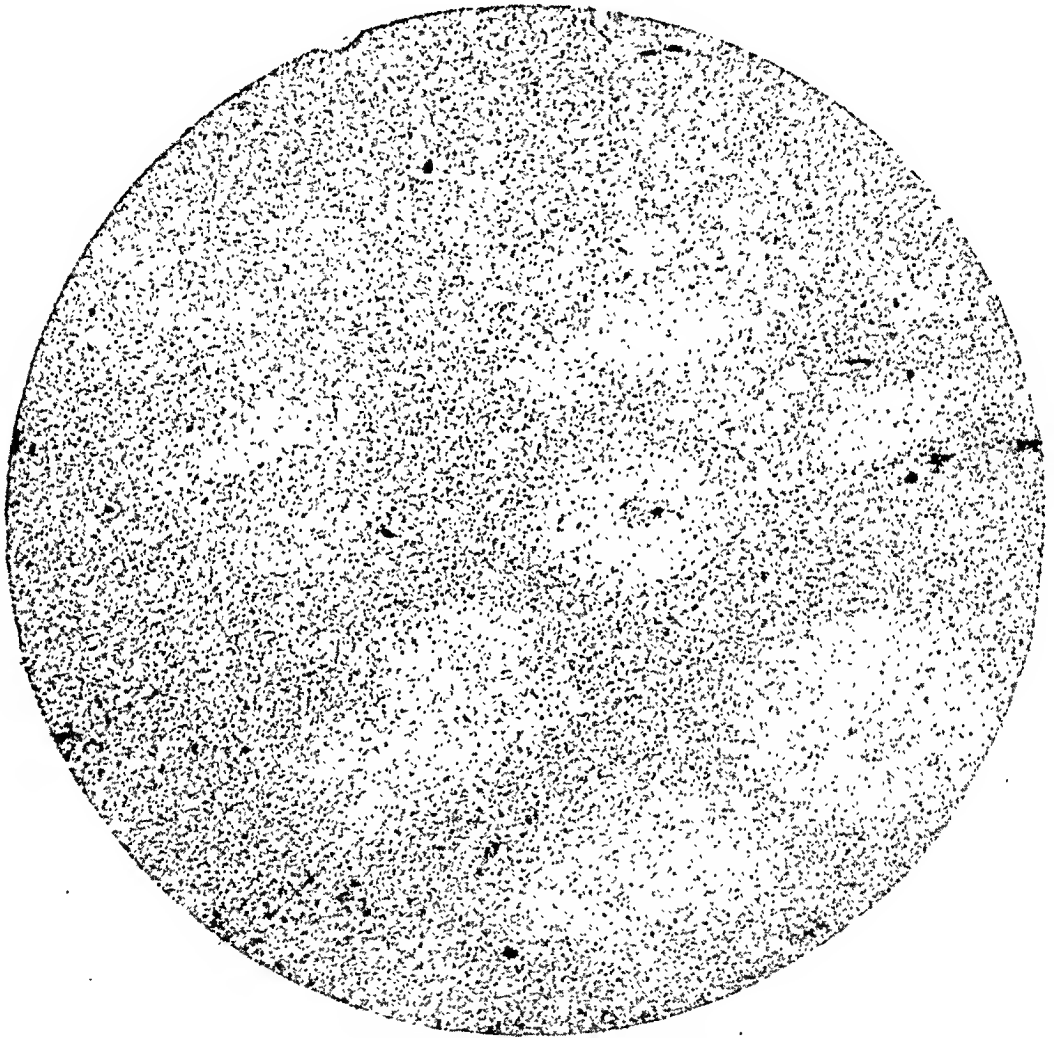


FIG. 3. Microscopic appearance of hemorrhage under low power showing numerous demyelinated areas around thrombosed blood vessels. Weigert-Pal  $\times 70$ .

The necropsy showed the dura mater to be under tension. The convolutions of the brain were flattened, the sulci were obliterated and the blood vessels were congested. The brain weighed 1450 gm. The ventricles were dilated and contained blood tinged fluid. The stained sections of the brain showed the typical microscopic picture of arsenical encephalitis. Examination of the other organs showed chronic myocarditis, luetic aortitis, congestion of the spleen, chronic vascular nephritis, and chronic hepatitis.

It was possible to obtain a history from the physician who was called in at the onset of the convulsions. This patient had been receiving injections of arsphenamine and the latest injection was 18 hours before the unheralded generalized convulsion.

*Case 3.* E. C., a white man, aged 33, was admitted to the Kings County Hospital on January 30, 1934. The day before he had remained at home because of severe headache, and the following morning while walking to the bathroom he collapsed. He was not unconscious, but was unable to get to his feet. Several hours after he

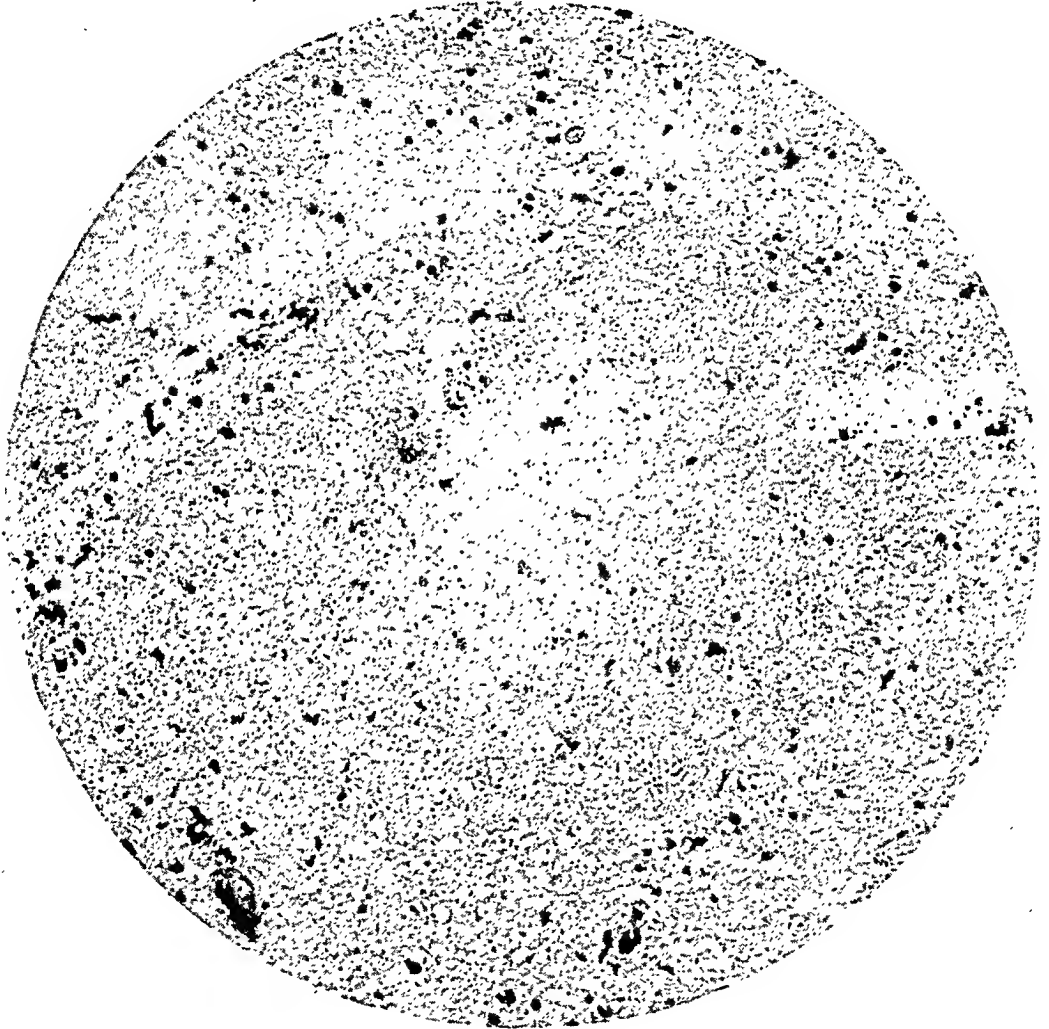


FIG. 4. An individual ring hemorrhage with central arteriole. Hematoxylin-eosin  $\times 300$ .

had been put to bed he became stuporous, began to scream and seemed to be choking. This was followed by convulsions.

On admission to the hospital, the patient was in coma. His face was flushed, the breathing was stertorous, and he was incontinent. The pupils were irregular, but reacted to light. The disc outlines were clear and the retinal vessels appeared normal. There was difficulty in opening the mouth, on which was dried blood from biting the

tongue. There was no rigidity of the neck. All the deep reflexes were active and equal. Bilateral Babinski response and ankle clonus were present. The spinal fluid pressure was 36 mm. of mercury, and the fluid was bloody.

The following morning the patient was stuporous but could be aroused. He talked rationally and recognized his relatives. He denied ever having had a venereal disease or that he had received injections of any kind at any time. The examination of the blood showed a white cell count of 9,450, with 69 per cent polymorphonuclear leuko-

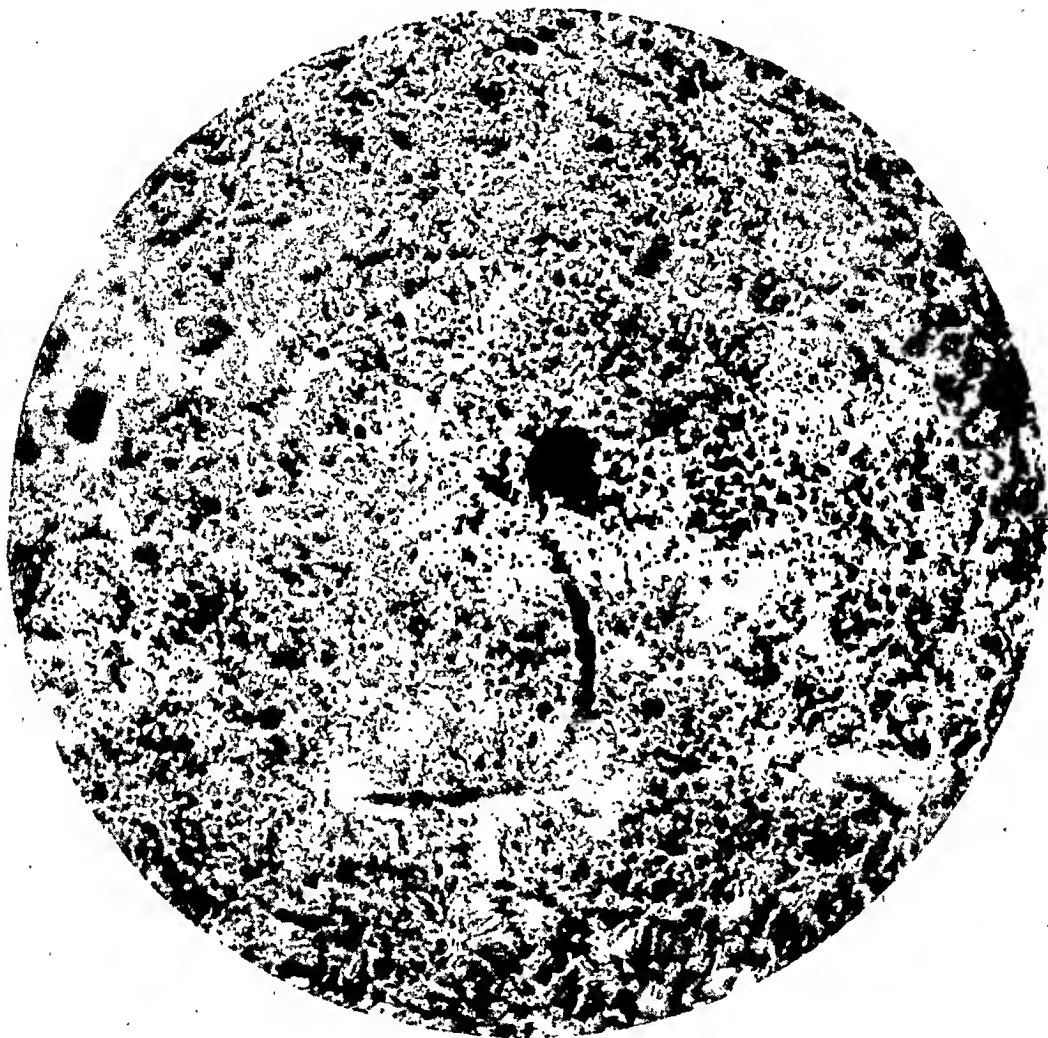


FIG. 5. A ring hemorrhage showing a central vessel which has ruptured with blood vessel leading to it. Hortega silver carbonate stain  $\times 300$ .

cytes. The clotting time was five and a half minutes. The blood Wassermann test was strongly positive. The blood urea was 35 mg., creatine 1.22 mg., and sugar 88 mg. per 100 c.c. The urine, spinal fluid, hair and nails were examined for arsenic which was found in the urine and nails. When the patient was told the result of the Wassermann test and that arsenic had been found in his urine and nails, he admitted that he had syphilis and had been receiving treatment for the disease. He had his last injection of arsphenamine two days before his admission to the hospital.

The temperature on admission was 101° F., and ranged between 101° F. and 102° F., until the fifth day when it reached 103° F. On this day râles and definite evidence of lobar pneumonia were found in the right lower lobe. These signs disappeared in six days, but the temperature continued to range between 100.4° F. and 101.8° F., until his death on the seventeenth day in the hospital.

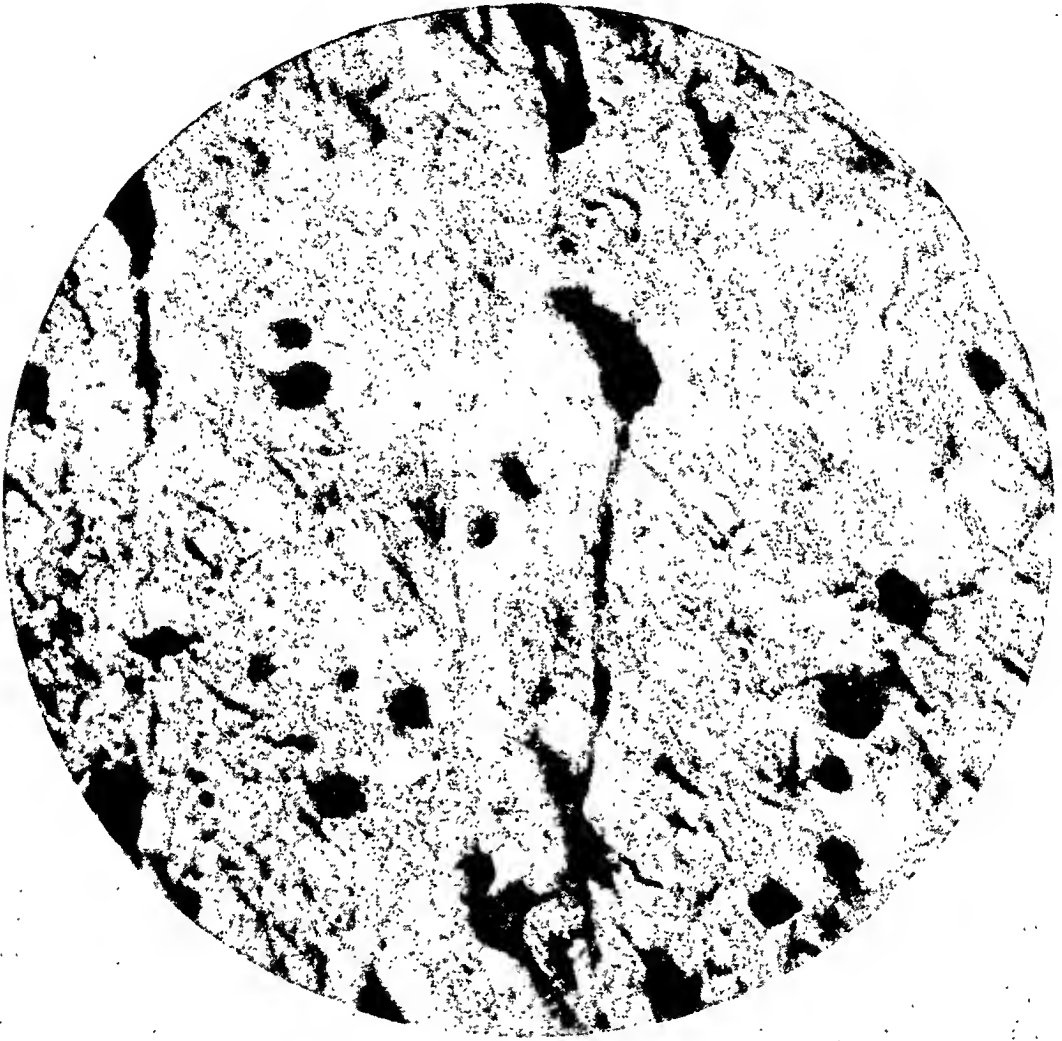


FIG. 6. Oligodendroglia cells undergoing degenerative changes  $\times 600$ . Globus modification of Hortega silver carbonate stain.

After regaining consciousness on the second day, he remained rational until the ninth day. During this time he gradually became deaf. He was drowsy and took very little interest in what was going on about him. In the second week he became very restless during his short waking periods. He was irrational. There were no other cranial nerve palsies and no weakness noted in his extremities. He developed tremors in the arms which continued for four days to within a few hours before his death.

At necropsy there was no evidence of pneumonia. The heart was somewhat increased in size, and the myocardium edematous and swollen. The liver showed a slight increase of fibrous tissue and its sinuses were filled with blood. The spleen was normal in size, dark slate in color. It also showed an increase of fibrinous tissue stroma. The kidneys appeared normal. There was a *marked pial and subpial* hemorrhage extending into the brain substance. The hemorrhage and softening involved the periphery of both cerebral and cerebellar hemispheres and scattered areas of somewhat symmetrical distribution. The stained sections of the brain tissue showed the typical picture previously described of arsenical encephalitis.

*Case 4.* J. P., a white man, aged 36, was seen in his home on March 16, 1934. His family stated that he had been receiving injections for syphilis at a clinic and that he had had his last treatment the day before. He had been working for weeks and had no complaints. He slept well the night after the last injection, but awoke with such a severe headache that he did not go to work. He remained in bed, and at 10 o'clock had his first convulsion. He did not lose consciousness but continued to have convulsions every 15 to 30 minutes. He became irrational, screaming, and it was necessary to hold him in bed. After several of these attacks it was noted by the family physician that there was weakness of the entire left side of his body.

When examined, seven hours after the onset, the patient was irrational, noisy, and extremely restless. The disc outlines were clear. The pupils were equal and reacted to light. There was a paralysis of the left side of his face, his left arm and left leg. The blood pressure was 118 systolic and diastolic 78. The temperature was 100.8° F.; the pulse 120. The patient was admitted to the Kings County Hospital. On the second day after admission to the hospital the convulsions stopped. The spinal fluid was blood tinged and under 24 mm. of mercury pressure. The spinal fluid and blood Wassermann reactions were strongly positive. Arsenic was present in the urine.

For eight days the patient was stuporous, but could be easily aroused. When aroused he was irrational and at no time recognized his relatives. The second week he became more restless and noisy, and on the eighteenth day he was committed to the State Hospital for the Insane. At the time of his commitment he had regained much of the use of his left arm and leg and his general physical condition was very good. I have followed the course of this patient in the State Hospital up to the present time. He has shown progressive deterioration mentally, although his physical condition still remains fairly good. He has almost full use of his left arm and leg.

Each of these cases demonstrates somewhat different points of interest in the toxic effects of arsphenamine. The first patient was pregnant, and Plass and Woods <sup>6</sup> have emphasized the point that, from their experience and from a review of the literature, pregnant women are more susceptible to the toxic effects of anti-syphilitic treatment by the modern arsenicals than are other individuals. Pritzi <sup>7</sup> believes that this susceptibility increases as term is approached.

The second case illustrates a clinical picture which, with the additional finding of blood in the spinal fluid, is frequently diagnosed subarachnoid hemorrhage. *Many errors have probably been made in the diagnosis of such cases.* The symptoms in our case appeared 18 hours after the injection and the patient died in less than 10 hours after the onset.

The third case illustrates the typical type of onset and the subsequent clinical picture, but here there was a prodromal symptom of headache preceding the collapse. These prodromal symptoms have been noted in several cases and although headache is the most consistently present symptom, men-

tal confusion seems to occur quite frequently. A recent patient in the Long Island College Hospital was confused for several hours prior to the attack, but was able to be up and was sweeping the sidewalk at the time of his collapse. This third patient denied having had syphilis or treatment for the disease, and although the clinical picture was typical of arsenical encephalitis the history of this case proves the necessity of a chemical analysis of the body tissues or excretions to establish the diagnosis. In this case the patient recovered from the acute onset and appeared to be improving, but after a few days he began to show a progressive mental deterioration which continued to the time of his death.

The fourth patient presented the typical type of onset with severe headache preceding the convulsion. In this case we have the neurological findings indicating localized brain damage. Although the general condition of this patient improved after his admission to the hospital, there was no improvement in his mental state and he shows progressive mental deterioration at the present time.

Our explanation for the pathological process is based on the several findings of Oliver and his co-workers, and those of Hanzlik and Karsner. The latter authors were the first to describe the agglutinating action of arsphenamine on red blood cells and later Oliver and Yamado demonstrated the agglutination of red blood cells, when placed on a slide after the administration of arsphenamine, and the formation of emboli in the brain and other special organs. Oliver also showed that the systemic blood pressure was first lowered after the administration of arsphenamine and that this fall is succeeded by a rise in blood pressure.

On this evidence is based our hypothesis that in the administration of acid arsphenamine there is first an agglutination of red blood cells which results in minute emboli in the vessels of the brain and other special organs. The blood pressure after the administration of arsphenamine is first lowered, but later elevated. The embolized and possibly weakened blood vessels may rupture in the stage of elevated pressure. This train of events seems to us to best explain the occurrence of the ring-hemorrhages.

The statistics of Cole <sup>s</sup> and his collaborators show that those patients who have latent syphilis are more apt to develop reactions than are those with early lesions. These authors also believe that young adults are more susceptible to the toxic effects of arsenical injections. Our experience with these cases leads us to hold the same opinion, and we wish to offer a word of caution in the use of arsphenamine in latent syphilis, especially in cases of pregnancy or where there is evidence of central nervous system invasion.

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## ARTHRITIS—A NEGLECTED DISEASE\*

By R. GARFIELD SNYDER, M.D., F.A.C.P., *New York, N. Y.*

ALTHOUGH it is increasingly evident that people are becoming more conscious of rheumatic diseases, and particularly arthritis, there still exists a woeful apathy and lack of accurate knowledge regarding these diseases, not only from the medical point of view but from the sociologic aspect as well.

It will probably be a distinct surprise to most readers to learn that an exhaustive national health survey<sup>1</sup> made in 1935–1936 by the United States Public Health Service, disclosed that among chronic diseases in the United States, "Rheumatism" ranks first in prevalence, second in producing disability and second in producing invalidity. While only fourteenth in causing death, rheumatism was found to produce more invalids than did heart disease and twice as many as all types of tuberculosis. More important, it led all other diseases, even heart disease, in duration.

The survey further showed that among the 127,000,000 persons in the United States, there are 6,850,000 cases of rheumatic diseases, 3,700,000 cases of heart disease, 930,000 cases of cancer and other tumors, 680,000 cases of tuberculosis in all its forms, and 660,000 cases of diabetes.

The significance of these figures cannot be minimized by suggesting, as many people believe, that most cases of rheumatic diseases occur in persons of advanced age. In fact, 50 per cent of the surveyed group were under 45 years of age and half of those permanently disabled were under 55 years of age.

The term "Rheumatic Diseases" is an all-inclusive one covering an almost unlimited number of variations, but in general the term is accepted to include any disease causing ache or pain in the ligaments, muscles or joints. Rheumatic diseases are known to be the oldest of which the world has any record. Indications of definite changes in the bone structure in and around the various joints, corresponding to what is today readily identified as osteo-arthritis, are apparent in the bones of Egyptian mummies. While they are most prevalent in those territories where dampness and cold prevail, they are not necessarily confined to any particular climate or section and as a group they play no favorites as to age, sex or type of individual. Thus, in children, we usually find acute rheumatic fever and a rarer type of arthritis known as "Still's" disease; as a rule, in the young adult up to 40, we may find various types of infectious arthritis (general and focal), and more often the dangerous and more crippling rheumatoid type; osteo-arthritis and gout are usually found in short, stout people past middle age, and still another variety, traumatic arthritis, is found in any type but usually it occurs in

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persons whose vitality happens to be temporarily or permanently at a low ebb, and is frequently common following a fall, injury or athletic strain.

Since it would be impossible to discuss the medical and sociologic aspects of the entire rheumatic disease group in a paper of this kind, consideration herein will be given only to certain forms of arthritis. In general, the various forms of this particular disease are more painful, last longer, are more difficult to treat and, when especially severe, are apt to cause more permanent invalidity.

A breakdown of such reliable statistics as the writer has been able to gather indicates that of the total number of 6,850,000 persons suffering from rheumatic diseases throughout the United States, over 3,000,000 (mostly adults) have arthritis. About 130,000 of these are completely disabled and consequently represent a total loss of some 45,000,000 work days of earning power; there are 800,000 partially disabled victims, of which over 50 per cent are estimated to lose an average of five months' work (approximately 60,000,000 work days) out of the year. Therefore, more than 100,000,000 work days are lost by completely and partially disabled victims combined. Reckoning this time at a minimum average of \$3.00 per day, we arrive at a wage loss alone of \$300,000,000 per year, exclusive of cost of diagnosis and care.

In the presence of such evidence of its importance, it is almost inconceivable how arthritis continues to be the most ignored and neglected of all chronic diseases, by the medical profession and laity alike. It is clearly entitled to be termed "Medicine's Neglected Stepchild."

From the medical standpoint, it is obvious to anyone interested in this subject that one of the main reasons for such neglect is the marked lack of knowledge of arthritis or of interest in this disease among general practitioners. The belief seems to be widespread throughout the profession that it is a progressive and incurable disease and that consequently any attempt at therapy would be a waste of time and effort on the part of the physician and of money on the part of the patient.

In answer to the first part of such criticism, i.e., that the disease is a progressive and incurable one, it is the opinion of those authorities who have been especially concerned with the treatment of arthritis for many years, that at least 75 per cent of all cases can be cured or greatly improved if properly diagnosed and treated during the first year of incidence. About 50 to 60 per cent might be cured or materially helped when attended during the second and third year. Naturally, the earlier a case comes to the attention of the qualified physician, the better are the chances for the normal resistance powers of the individual to play an important rôle in recovery. On the other hand, just as in any other chronic disease, the longer the duration, the greater and more serious its cumulative effects on the general systemic condition of the individual and the lesser the chances of successful cure or improvement. Nevertheless, unlike the almost inevitable fate of a long-suffering tuberculosis or cancer patient, any of the leading authorities of

today can produce case histories to prove that even in longstanding, apparently hopeless cases, rehabilitation sufficient to return the victim to his former gainful occupation is often possible.

Specific data as to exact results and percentage of cures effected in this country are not available because as yet it has not been possible for all our hospitals and clinics to establish generally satisfactory follow-up systems, a condition which to a great extent is due to a peculiar reticence on the part of the patients. Except for a most exhaustive and complete effort to follow the clinical and life course of a large group of arthritis patients made by Dr. H. A. Nissen at the Robert Breck Brigham Hospital of Boston during the period from 1914 to 1934,<sup>2</sup> whatever statistical data the writer could find were largely representative of results obtained by physicians in private practice.

The results of Dr. Nissen's study disclosed that while from 15 per cent to 20 per cent of all cases of arthritis are apt to take a progressively backward course despite any and all forms of treatment, "in any group of so-called arthritics, 68 per cent or more can be assured of improvement." \*

Furthermore, statistics from Sweden are very complete in this respect. There the care of the chronic rheumatism patient has developed to a most advanced stage. Nine free hospitals of some 60 beds each are devoted exclusively to their treatment. Cases are closely followed up sociologically for long periods after patients are discharged. The Swedish figures indicate that three years after discharge, 60 per cent of the patients are working at their former occupations and a further 18 per cent have been rehabilitated to such an extent that they require no further social aid.

While the criticism as to the futility of any attempt at therapy has been partly answered by the preceding statistics as to curability, the following might assist in further clarifying the subject and dispelling existing doubts as to the nature and value of treatment.

The term "arthritis" embraces a certain group of rheumatic diseases in which the most evident symptoms appear in the joints. In general, the various types of arthritis can be classified into two main groups, i.e., those of which the causative agent is known and those in which the exact causative agent has never been determined.

Whether the type is of known or unknown origin, one cannot over-emphasize the need for early and accurate classification of all arthritis cases, together with prompt and appropriate treatment, which usually should include complete mental and physical rest if at all possible, and relief from the worry of financial obligations. Temporary cessation of occupation is often desirable and frequently vital.

Since optimum results can be obtained only by the efficient application of such medical and physical measures as are known to be of value, it should be obvious that prolonged and careful study must be given by any physi-

\* This group is being followed to date. The results of the 1935 to 1938 follow-up have not as yet been published.

cian to acquire the ability, judgment and experience necessary properly to segregate and classify cases and equip himself to cope effectively with those that present unusual characteristics or require extraordinary measures.

The forms of arthritis of known origin comprise only about 25 per cent of the total number of cases, and the number of these with which any doctor is likely to come in contact, either in office or clinical practice, is extremely limited. Inasmuch as they can usually be solved by the application of accepted forms of specific treatment, they do not present particularly difficult problems. The remaining 75 per cent of all cases fall into the group of unknown origin which includes rheumatoid arthritis, infectious arthritis—either focal or general—osteo-arthritis, and gout. All of these types are extremely variable in nature and, with the exception of gout, no specific form of treatment can be prescribed for them.

From the layman's point of view, the apathy and neglect can be attributed to several factors, chief among which has been the lack of education and publicity regarding the possible dangerous implications of such common complaints as the growing pains of children, the repeated muscular pains, undue fatigue and general feeling of lassitude of the young adult, or the stiffening and aches in the joints of the elderly. Any or all of these manifestations might well be definite early symptoms of a serious type of arthritis which, just as in tuberculosis and cancer, should be attacked in their earliest possible stage of development.

Whether unwittingly or by necessity, many people either neglect such potential early symptoms or futilely try to doctor themselves, often with the aid of questionable "quack" methods, "short-cut" cures, patent medicines and home diathermy.

A survey of chronic diseases in the State of Massachusetts<sup>3</sup> made by G. H. Bigelow and H. L. Lombard in 1931, showed that of the total number of 140,000 persons suffering from chronic rheumatism in that State, less than 30 per cent were directly under medical care; the remaining 70 per cent were either attempting to treat themselves or were receiving no treatment at all. Many of these people had lost confidence in the curative value of the treatment they had previously employed, others were unable to finance the cost of care.

Unfortunately, the incidence of arthritis among the poor is about 50 per cent higher than among the well-to-do. Many poor people who might realize the dangers involved in delaying adequate treatment are unable to pay for it. We thus come to the last and probably the most important reason for the present unsatisfactory status of the arthritis problem, *the lack of facilities*.

In an effort to determine the nature and extent of existing facilities throughout the United States, the writer undertook to make as thorough a survey as possible of physicians, hospitals, clinics and other reliable sources of information. This survey disclosed the following:

Unlike the situation with respect to certain other chronic diseases, par-

ticularly tuberculosis, the arthritis victim lacking the means to finance his treatment is almost entirely dependent on the personal interest, resources and facilities of private hospitals and physicians.

At present little if any provision is made in the average general hospital program for the chronic arthritis patient. A general hospital may have facilities for free emergency cases, but no voluntary and hardly any public hospital can treat or help an arthritis victim free of charge long enough to do him any appreciable good. Furthermore, a general hospital and its staff often look upon these patients as nuisances; little interest is shown in them compared to that taken in patients suffering from acute diseases of a more spectacular nature offering prospects of rapid cure. There is a feeling of futility in attempting to help the victim of chronic arthritis.

Throughout the entire United States there is no hospital or institution devoted exclusively to the treatment of arthritis. Most private hospitals in the larger cities do maintain some degree of facilities for arthritis patients. In Boston, New York, Philadelphia, Chicago, Rochester, Minn., Ann Arbor, Michigan, St. Louis, Hot Springs, Ark., Tucson and San Francisco, for example, there are outstanding and well-organized clinics for arthritis. However, very few of such hospitals or clinics can treat or hospitalize their patients free of charge. There are also a number of well-known and splendidly equipped spas in the United States to which the well-to-do can repair for treatment and cures. At Saratoga Springs, N. Y., the State provides treatment facilities comparable to the best in the world and, although these facilities are available to needy patients of the State free of charge upon their physicians' certification of eligibility, no hospitalization is provided and such patients therefore must bear the not inconsiderable expense of room and board themselves. Furthermore, while it is true that many state and county hospitals endeavor to make some provision for poor patients suffering from rheumatic diseases, whatever facilities are available often are contingent upon such admittance conditions and requirements that the number of dependent chronic arthritics actually hospitalized or adequately cared for is negligible.

Compared to the staggering economic costs of arthritis, practically no funds or facilities of any importance are available from outside sources to help the medical profession attack the disease. Except for the specific grants listed below, all hospitals, clinics and spas in the United States at present caring for arthritis victims operate entirely at their own expense:

The Robert Breck Brigham Hospital of Boston has 25 free beds available.

The Massachusetts General Hospital of Boston has 25 beds supplied by the Commonwealth of Massachusetts and a donation of \$30,000 per annum from a private source which is used for research.

The Leo N. Levi Memorial Hospital of Hot Springs, Arkansas, has 75 free beds, together with a complete clinical and research department.

The Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital in New York City receives an income of approximately \$15,000 per year which is devoted almost exclusively to research. No free beds are provided.

The Research Hospital for Chronic Diseases, Department of Hospitals, New York City, has 10 or 12 beds available for patients suffering from rheumatoid arthritis.

Bellevue Hospital, New York City, has from ten to thirty beds set apart and constantly occupied by patients suffering from rheumatic diseases.

The Cornell Medical Center of New York City receives an annual endowment of \$25,000 for research.

The University of Michigan has the use of the income from \$1,000,000 per annum for research, but at present no free beds are available.

Thus, as far as could be determined, there are not more than 200 free beds specifically available today for arthritis victims unable to pay, and not more than \$200,000 is provided from outside or private sources to help finance the research so vitally important successfully to combat the disease. Compared to the figures of more than 100,000 free beds and over \$100,000,000 available for research in tuberculosis and the care of its victims, the vast disproportion appears out of all reason.

As a result, up to the present time many physicians who might be interested in learning more about the problem of arthritis are handicapped by the almost complete lack of facilities for postgraduate study and research in chronic rheumatic diseases. It is significant that of a total number of 77 recognized medical colleges in the United States, as far as the writer could determine there are but six (Harvard, Cornell, College of Physicians and Surgeons, New York University, University of Michigan and the University of Pennsylvania) which offer opportunities or facilities for the specialized study of these diseases. The University of Pennsylvania is the only one of these colleges that offers an opportunity for postgraduate study in the treatment of arthritis. Its course, which is under the direction of Dr. Ralph Pemberton and his associates, is well organized, has abundant material and affords excellent training to any doctor interested in improving his knowledge regarding the most efficient methods of treating the various types of arthritis. This course probably represents the first organized teaching on the subject available in the country.

At first glance the results of the writer's survey would seem to be far too discouraging to warrant the hope that any material improvement of existing conditions might be possible. However, if it is recognized that the problem is far too vast for the medical profession to handle alone and that it is a sociologic one requiring the combined interest, efforts and assistance of society at large, the handicaps involved are certainly no greater than those confronting the other chronic diseases in the past which have been successfully and even spectacularly overcome.

The marvelous progress made against tuberculosis during the last 35 years is an outstanding example of what can be done. Up to 1904, that disease was very definitely on the offensive and no united defense, voluntary or official, had been made against it. Of course, the spectacular starting point of its crusade was Dr. Trudeau's courageous personal campaign against

the disease. This accomplished much to arouse interest and led to the establishment of the first small sanatorium at Saranac, N. Y. However, quickly following upon the noted achievements of Dr. Trudeau and others, a group of 400 far-sighted physicians and laymen organized the National Tuberculosis Association, which, although handicapped by a general lack of interest and funds, nevertheless took prompt aggressive action. Faced with the added incentive of having the next meeting of the International Congress for the Study and Control of Tuberculosis in New York in 1905, they successfully appealed to the Russell Sage Foundation. It was largely the financial assistance received from that organization during the following ten years that enabled the Tuberculosis Association to organize successfully its campaign for a national crusade which has resulted in the widespread interest and coöperation clearly indicated by the enormous resources and splendid facilities for research and treatment available today throughout the entire country.

The nature of the arthritis problem in this country today presents a close parallel to the early conditions confronting tuberculosis. Brilliant pioneers have been active since as early as 1904. For instance, Dr. Goldthwaite and his associates, Drs. Osgood and Painter of Boston, made valuable contributions on the importance of rest and posture in the prevention of deformities associated with arthritis. Drs. Billings and J. Miller of Chicago made equally valuable contributions, the former on the importance of focal infection and the latter on the relative value of non-specific vaccines; Dr. Pemberton of Philadelphia, an outstanding leader in arousing greater interest in arthritis, emphasized the importance of restricting the diet and the possible rôle of carbohydrates. Drs. Richardson and Nichols published an important article on the pathology of the joints.

Furthermore, largely influenced by the Mayo Foundation, definite efforts to develop a widespread awakening of interest among the members of the profession have been under way for the past ten years. In this connection, a brief review of the history of the problem in Europe as it ties up with activity to date in this country might be of interest. Parenthetically, although the level of medical effort in combating arthritis is probably higher in the United States than it is anywhere else in the world, authorities both here and abroad are unanimously agreed that we thus far rank far behind in a proper appreciation of its sociologic and economic importance. Such lack of interest would seem to be substantiated by a survey made of our leading insurance companies to determine the extent of the admitted heavy demands made upon them for disability payments arising from arthritis. Practically without exception, no serious attempts had been made by these companies to break down their statistics and as a result it was impossible to obtain reliable information regarding incidence and economic costs from those presumably well-informed sources.

In England after the World War, the insurance companies were largely instrumental in directing attention to the alarming incidence and cost of

rheumatic diseases there. A report prepared at the instigation of the British Ministry of Health in 1924 by Dr. J. Alison Glover fully confirmed their astounding incidence and pressure on industrial workers as well as the economic losses involved. General interest was aroused which eventually resulted in the organization of an International League for the Study and Control of Rheumatic Diseases (*Ligue Internationale contre le Rheumatisme*). Most European countries quickly became acutely conscious of the economic importance of the problem and many national societies are today strongly attacking it with, in many cases, important financial assistance from outside sources. Many of the European societies publish journals devoted exclusively to activities in rheumatic diseases at home and abroad, thus maintaining general interest.

Recognizing the desirability of a mutual exchange of ideas with the United States, Dr. Van Breeman of Holland, while he was president of the International League in 1928, asked Dr. Louis B. Wilson, Director of the Mayo Foundation, to suggest names for an American Committee. In collaboration with two Mayo colleagues, Drs. Henderson and Hench, and Dr. Osgood of Boston, Dr. Wilson selected a tentative group of men, all of whom, because of the high character of their work, university affiliations and professional writings, had indicated a sufficiently deep interest in the arthritis problem to constitute a representative American body. This group became the American Committee for the Control of Rheumatism and its first meeting was held early in 1928 with Dr. Pemberton as Chairman and Dr. Henderson as Secretary. The other members of this first committee were Drs. Osgood, J. O'Reilly and Zinsser of Boston, L. Barker of Baltimore, C. C. Bass of New Orleans, R. Cecil of New York, R. Haden of Cleveland, Joseph I. Miller of Chicago, and Rea Smith of Los Angeles.

The International League for the Study and Control of Rheumatic Diseases (*Ligue Internationale contre le Rheumatisme*) is to hold its next annual conference in this country in 1940. It is hoped that by that time sufficient progress will have been made in the development of a general arthritis campaign so that as creditable a showing will be made at that meeting as was made by the National Tuberculosis Association at the first International Congress on Tuberculosis held here in 1905.

During the years 1930, 1931 and 1932, the American Committee met on the first day of the annual meeting of the American Medical Association. Physicians of high caliber, known to be interested in arthritis, were invited to attend these meetings. Attractive programs were offered which consisted in the presentation and discussion of a necessarily limited number of papers and the sponsoring of exhibits on arthritis simultaneously with the exhibits presented by the American Medical Association on other subjects. At a later date, all the papers read at these meetings were published in the form of a Symposium on Arthritis.

In 1933, through the efforts of the Committee, the American Rheumatism Association was formed for the specific purpose of promulgating and

exchanging ideas among professionally qualified students of rheumatic diseases, encouraging intensive study of them, and spreading sound doctrines of prevention and treatment.

This Association has proceeded cautiously in its expansion, adhering to rigid qualifications for membership in order to maintain the highest possible medical standards. As a consequence, its present membership is not large, although from an original number of 26, it now has slightly over 200 members.

Every year since its formation the Association has appointed a Reviewing Committee comprised of members representative of a cross-section of the country, which unselfishly devotes a great amount of time and effort to the review of more than 600 articles on arthritis which have appeared during the year in English and American literature. This year's Reviewing Committee is comprised of Dr. Hench of Rochester, Minn., W. Bauer of Boston, R. Dawson of New York, Holbrook of Tucson, J. A. Key of St. Louis, and Francis G. Hall of Boston. Worthwhile abstracts of all articles reviewed and comment thereon appear annually in the *ANNALS OF INTERNAL MEDICINE*.

As further indication of the extent of activity, it should be mentioned that both the American Committee for the Control of Rheumatism and the American Rheumatism Association have the important and most cordial support of the American Medical Association, which has opened its programs and Journal to an increasing number of reports on arthritis, thus bringing important developments and activity in that field to the attention of its more than 150,000 subscribers.

A few papers of special interest to laymen are published annually in *Hygeia*, and the American Rheumatism Association has created associate memberships for interested laymen, social workers, insurance executives and members of professions allied to medicine. All these associate members receive bulletins summarizing information of current interest in arthritis.

From the foregoing outline of activity in this country, it is obvious that interest on the part of the medical profession has not been exactly dormant with regard to the arthritis problem. The framework for the start of a campaign has been erected. We must now proceed to build upon this framework and develop a permanent structure. This development should follow four main lines, i.e., (1) publicity; (2) education of general practitioner; (3) improvement of existing facilities and (4) research.

As a first step, the incidence, personal dangers and devastating economic consequences of arthritis should be dramatized and so forcefully emphasized to the public that the extreme need for increased interest and action will be clear to everyone. To do this most effectively, a small publicity department, preferably as an adjunct to the existing American Rheumatism Association, should be established without delay. This department should avail itself of such facilities as the radio, press and popular magazines to help drive home its objectives.



Along with such publicity, the American Rheumatism Association should sponsor and encourage further postgraduate education of the general practitioner by means of lectures, exhibits, bulletins, journals and actual contact with recognized, well-organized and efficiently operated arthritis clinics. Increased efforts should be made to interest properly qualified physicians to join the Association.

Every large general hospital which at present has clinical facilities for the treatment of arthritis should be impressed with the need of having such facilities conform to the Minimal Standard Requirements for Arthritis Clinics established by the American Rheumatism Association. A feature of these Requirements which would be of inestimable value would be the provision of a certain limited number of free beds in each hospital devoted exclusively to the detailed study and treatment of certain arthritis cases by the staff of the Arthritis Clinic connected with the hospital. Later, the development and establishment of new clinics and facilities conforming to the Minimal Standard Requirements should be considered. As such present and future clinics are duly recognized, arrangements should be made to have them listed in the Hospital Number of the *Journal of the American Medical Association* under the caption "Annual Presentation of Hospital Data."

Simultaneously with such efforts to improve existing facilities, the cooperation and financial assistance of private patients and philanthropists must be obtained in order to carry on the all-important research as to the causes of arthritis and the study of present and new methods of treatment.

In conclusion, the writer must express his conviction that in his opinion, there is nothing more satisfying to the physician than the gratitude of a rehabilitated arthritis patient, and that there is no finer or more worthwhile medical task than the control of a disease which exacts such an astounding toll from the community. However, from past experience in other crusades against chronic disease, it is known that the medical profession, no matter how outstanding its men, brilliant their research and high their ideals, can accomplish little by itself. All available resources must be combined as quickly and effectively as possible to combat the continued ravages of arthritis and assure the rehabilitation of an ever-increasing number of its victims.

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# OIL ASPIRATION PNEUMONIA AND PNEUMOLIPOIDOSIS \*

By PHILIP G. C. BISHOP, M.D., *New York, N. Y.*

THE classical case reports and animal experiments of Laughlen <sup>65</sup> in 1925 dealing with a "specific" lung reaction to aspirated oil and lipoid substances have awakened considerable interest in clinical, pathological and experimental aspects of this subject.

It is hoped that a summary of the cases found in the literature to date, together with a report of new cases, will upon analysis indicate certain trends that may be useful (1) in guiding the clinician to earlier recognition of this rare disease; (2) as a stimulus to further studies and correlation of the facts found; (3) in offering suggestions in prevention and treatment.

## TERMINOLOGY

The term lipoid pneumonia is probably the one that is most frequently employed at present. Inasmuch as most of the cases reported clinically or at autopsy show some degree of pneumonia, it is perhaps reasonable that this term should be included in naming this disease. Again, inasmuch as the etiological agent is either an oil (mineral oil) or a lipoid (vegetable or animal) either the term "oil" or "lipoid" should logically be included. Third, the disease is usually produced under conditions favoring aspiration of the offending agent. Therefore, the term "oil aspiration pneumonia" (Ikeda <sup>53, 54</sup>) seems suitable when the offending agent is a form of mineral oil. However, when the offending agent is a true lipoid, the author prefers the term "pneumolipoidosis"—a term which denotes the organ involved, the causative agent, and the accumulation or increase of lipoids in the pulmonary parenchyma—free or intracellularly. This latter term also becomes available for the few cases in which there is no pneumonia due to bacterial infection, and where the lipoidosis may be of endogenous nature, as suggested by some authors.<sup>19, 51, 55</sup>

"Oil aspiration pneumonia" and "pneumolipoidosis," therefore, broadly cover the various phases of this clinico-pathological picture.

## INCIDENCE

An exhaustive search of the literature to date reveals 136 cases (tables 1 and 2) either *mentioned* or fully reported, the majority of which were diagnosed at autopsy. These reports were made in a period of 12 years from 1925 to 1938. However, some of the pathological material from

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TABLE I  
Authors and Oil Aspiration Pneumonia Cases as Reported

Year	Author	Number of cases	Year	Author	Number of cases
1925	Laughlen, G. F.....	5	1935	Karelitz, S.; Denzer, B. S....	1
1926	Thomas, W. S.; Jewett, C. H.	1	1935	Langdon, J.....	1
1927	Pinkerton, H.....	6	1935	Normand, P.....	1
1930	Valobra, N.....	1	1936	Ball, F. E.....	1
1931	Brüning, H.....	1	1936	Baumgartner, L.; Angevine, D. M.....	3
1932	Pierson, J. W.....	4	1936	Davis, K. S. (one identical with that of Houck).....	3
1932	Pollak, B. S.; Potter, B. P...	1	1936	Houck, G. H.....	1
1933	Bodmer, H.; Kallos, P.....	1	1936	Klinck, G. H., Jr.....	1
1933	Fischer-Wasels, B.....	1	1936	Reineke, H. G.; White-leather, J. E.....	4
1933	Meursing, F.....	2	1936	Ritchie, G.....	12
1934	Ellinger, E.....	3	1936	Tchertkoff, I. G.; Ornstein, G. G.....	10
1934	Goodwin, T. C.....	25	1937	Brenner, F.; Urban, F. F....	2
1934	Grayzel, D. M.; Du Mortier, J. J.....	3	1937	Fetterman, G. H.....	2
1934	Hayes, J. N.; Gardner, L. U.	3	1937	Ikeda, K.....	5
1934	Rabinovitch, J.; Lederer, M.	6	1938	Paterson, J. L. H.....	8
1935	Boyd, W.....	1	1938	Bishop, P. G. C.....	3
1935	Cannon, P. K.....	1			
1935	Garrison, H. F.....	1			
1935	Graef, I. (read).....	6			
1935	Ikeda, K.....	7			

Total cases = 136

TABLE II  
Oil Aspiration Pneumonia

Total number of cases of oil aspiration pneumonia	136
A. Living cases	20
I. Cases diagnosed as oil aspiration pneumonia in life	23
1. Cases diagnosed and living	20
2. Cases dead but diagnosed in life	3 (Baumgartner and Angevine 2, Davis 1)
B. Patients who died	116
II. Cases autopsied	112
3. Cases diagnosed in life and autopsied	2 (Baumgartner and Angevine)
4. Material obtained by bronchoscopy (post mortem)	1 (Reineke and Whiteleather)
III. Pathological examination not specified	2 (Pierson)
IV. Cases without autopsy	2 (Reineke and Whiteleather 1, Davis 1)

which the diagnoses were made dates back at least to 1902 (Normand's case,<sup>71</sup> also reviewed by Comby<sup>19</sup>). When this present total of cases is compared to the enormous quantity of lipid agent used medicinally, as dispensed by hospitals, institutions, drug stores, and private physicians throughout the country and the world, the incidence of the disease entity becomes numerically insignificant. Rarity of occurrence is further brought out by the fact that Laughlen<sup>65</sup> added a fifth case to his series of four only after a search through 300 autopsy cases in the year preceding his report. Pinkerton<sup>76</sup> found six cases in a search through 290 consecutive autopsies, and Ikeda reports a case of "chronic oil aspiration pneumonia" in an adult woman, the only one found in several thousand necropsies in the past several years. On the other hand, a number of cases have remained undiagnosed

in life and at autopsy, and some diagnosed cases have not been reported. Therefore, it is well to be conservative in comments on statistics until a larger series of bona fide cases has been collected.

### DIAGNOSIS

As yet the diagnosis during life is not dependent upon *one* or *several distinctive diagnostic* features, but a strongly presumptive diagnosis is arrived at by elimination in differential diagnoses. This is even true perhaps in the case of the so-called typical chest roentgen-ray. Barring certain variations the diagnostic features are by and large similar in children and adults. The onset is insidious. The disease is rarely uncomplicated. The patient is first seen due to another disease or complication. The majority of the cases occur in the period of infancy up to two years of age, with a second rise in the age group of beginning debility, the fifth and the sixth decades (figure 1).

#### AGES OF OIL ASPIRATION PNEUMONIA CASES

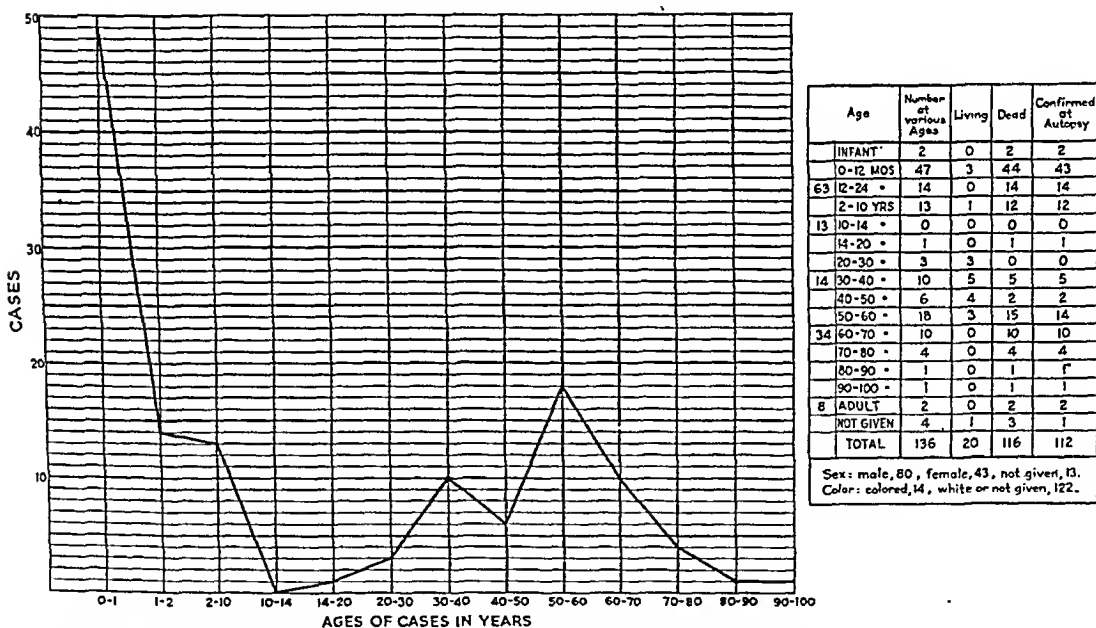


FIG. 1. Showing the preponderance of cases occurring in the first year and the sixth decade.

### HISTORY

The special facts to be obtained from the routine systematic history are, of course, detailed information on the use of an oily or lipid agent. Not only should the quality of the agent be known (table 4) but also the amount, the frequency, and the duration of its use. Furthermore, the mode of administration should be inquired into (figure 2), whether by mouth, pharynx, nose or by trachea; and the position of the patient during administration

should be determined. Inquiries about feeding difficulties or conditions favoring aspiration of food should be made in order to rule out the lipoids of food as a possible causative agent. If the additional trouble is taken to make such inquiries in all cases that present atypical and prolonged pulmonary disorder, an early clue to a possible instance of this disease may be obtained. When the volunteered symptoms have been given, further specific inquiry into symptoms and conditions that may favor aspiration should be made. Such inquiry may reveal reduction or abolition of the swallowing or cough reflex.

#### MODES OF LIPOID AGENT ADMINISTRATION (TOTAL CASES = 136)

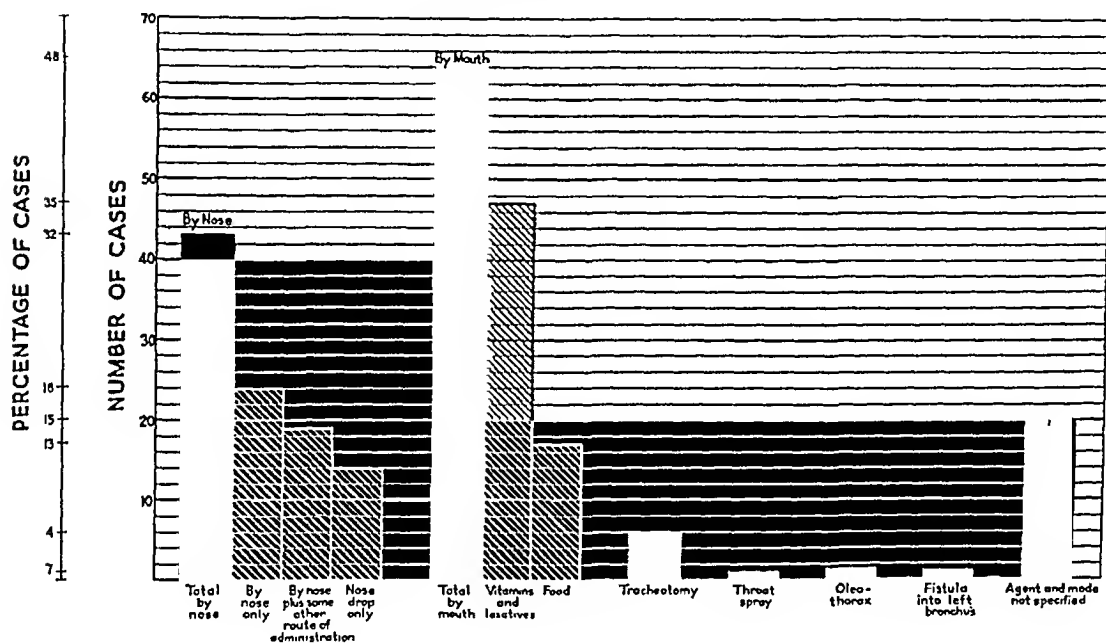


FIG. 2.

A history of cough, choking, gagging, regurgitation, vomiting and hic-coughing is frequently given. Such conditions are factors in enhancing aspiration (table 3).

Immobility and recumbent position, especially if prolonged, are noteworthy, inasmuch as insidious aspiration is at least more favored in the flat position than when the patient is erect or ambulatory.

#### PHYSICAL EXAMINATION

There are no specific diagnostic signs. As Goodwin<sup>38</sup> says, such signs as may be found are difficult to evaluate inasmuch as the condition is usually accompanied by some other and more severe illness or complication.

The nutritional and developmental status of the patient is usually impaired. Children, as observed by Goodwin,<sup>38</sup> are frequently stunted in

TABLE III  
Symptoms or Conditions Which May Favor Aspiration

	Conditions or symptoms found. Number of cases	Conditions or symp- toms found during period of lipid agent administration. Number of cases
Cough.....	51	40
Vomiting.....	42	31
* Impaired general condition.....	39	39
Difficult feeding.....	34	22
On back in bed.....	17	14
Dysphagia.....	17	13
Convulsions.....	15	7
Coma.....	11	6
Gagging.....	10	2
Choking.....	8	6
Stupor.....	6	3
Paralysis.....	4	4
Subdued reflexes.....	4	3
Never sat alone.....	2	2
Plaster cast—unable to hold head, sit alone.....	2	2
Twitchings.....	1	1

\* Including: "Failure to gain, underweight, underdevelopment, nutritional disturbance, malnutrition, emaciation, marasmus, inanition, weakness."

growth, and wasting and emaciation are frequently recorded. In the more severely ill patients various nervous disorders such as irritability, convulsions, listlessness, stupor, and coma have been observed. Rapid respirations are a frequent finding, in children usually without dyspnea, and in adults with occasional cyanosis. Clubbing of the fingers has been found in several cases but is more likely accompanying chronic pulmonary diseases.

Fever is present but its degree and course are not typical. The pulse is as variable as the fever and may be disproportionate to it. Upper respiratory infection is frequently present. Examination of the chest reveals a variety of signs. There is always a varying degree of impaired resonance, especially over the lower inner chest areas of one or both sides, and usually there are bronchial or parenchymal râles. As the condition progresses these signs will persist with relatively minor variations. Marginal or over-lying emphysematous breath sounds may be heard. These findings are frequently confused by the signs of other complicating lung disease. Occasionally findings associated with right heart failure secondary to extensive pulmonary fibrosis may be present. Enlargement of the spleen and lymph glands is found not infrequently without apparent clinical causal relationship (figure 3).

#### ROENTGEN-RAY

The most important diagnostic aid to date is the chest roentgen-ray appearance (figures 6, 7, and 8). This is brought out by several authors,<sup>84</sup> but in particular by Goodwin.<sup>38</sup> What may be considered a typical roentgen-ray is one that shows a shadowing found in the peri-hilar region, bilaterally or unilaterally, which reaches towards the peripheral lung fields depending

TABLE IV  
Lipoid Agent and Identification of Oils

	Agent	Identification	Looked For But Not Found
Mineral oil	59 24 3 3	20 (a) 3	1
		Mineral oil (paraffin, liquid petrolatum, albolene, nujol, etc.)	
		Mineral oil in combination	
		Not specified, but probably mineral oil	
		Not specified, but probably mineral oil in combination	
		<u>89</u>	
		Total: Mineral oil used with or without combination	
Food fats	1 11 1 1 2 7	1 1 1 1 (Butter fat)	
		Cream	
		Milk	
		Egg yolk	
		"Oil and fat"	
		Food	
		Probably food	
		<u>23</u>	
		Total: Food fats	
		Cod liver oil	
		Haliver oil	
		Viosterol	
		<u>37</u>	
		Total: Vitamins	
Non-mineral oils	2 1 1 1 1	(b) 8 1 2	1
		Castor oil	
		Olive oil with ephedrine inhalant	
		Glycerine with vaseline	
		Gomenol	
Non-lipoids given with lipoid agents	1 1 1		
		Argyrol	
		Neosilvol	
		Silver nitrate	
		Denied by history	
		Lipoid agent not stated	
		<u>39</u>	
		Ephedrine jelly	
		Paraffin with menthol	
		Liquid petrolatum with menthol	
		Liquid petrolatum with thymol and menthol	
Medicated lipid agents	6 16	2	1
		(a) Liq. petro. Paraffin oil Mineral oil	
		(b) Plus butter fat 1 Plus liq. petro. 2 Plus mineral oil 1	

COINCIDENT DISORDERS AMONG 128 OIL ASPIRATION PNEUMONIA CASES

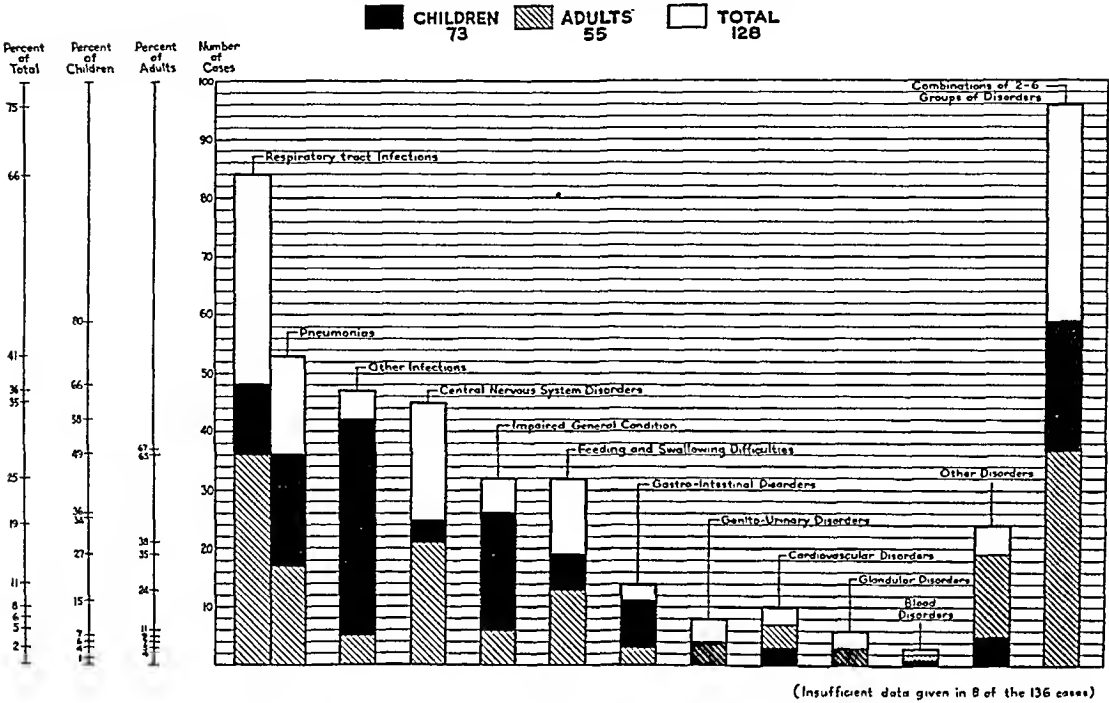


FIG. 3.

DIAGNOSTIC FEATURES OF OIL ASPIRATION PNEUMONIA CASES  
TOTAL LIVING AND DEAD

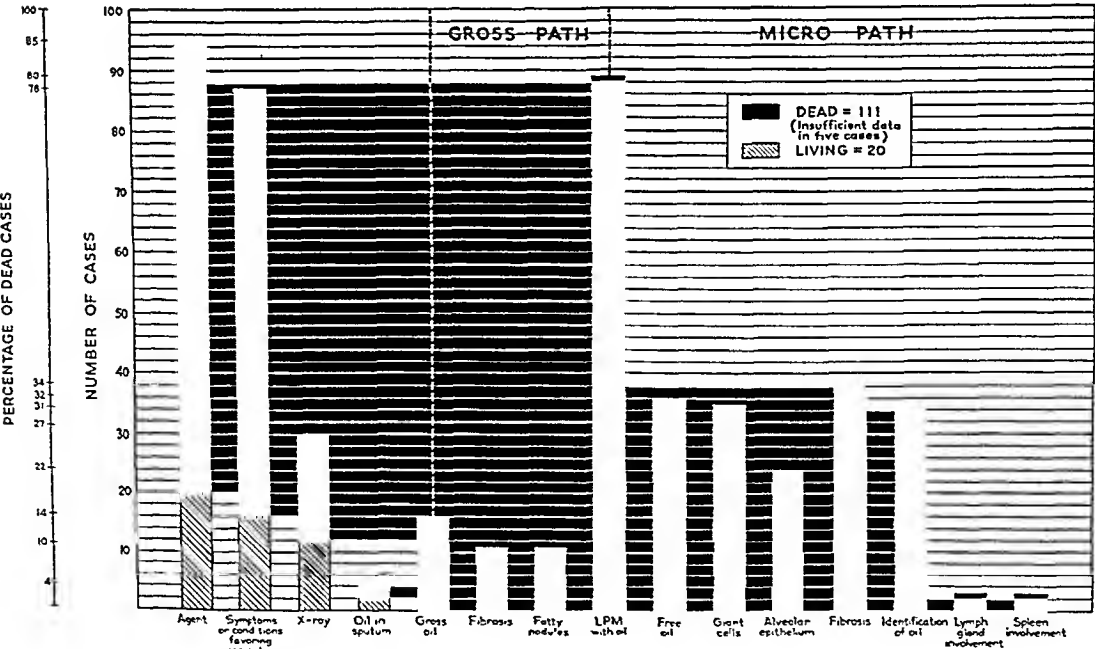


FIG. 4. Note that by far the majority of cases have been diagnosed on three factors: Agent, symptoms favoring aspiration, and the presence of large phagocytic monocytes containing oil droplets found on microscopic section of the lung at autopsy.



upon the duration and extent of the disease. The opacity may vary in quality from a more or less central consolidation almost of the quality of calcification, to a fine haze which towards the periphery is barely denser than normal lung shadows. There is, therefore, an outline of involvement usually without sharp demarcation. Pneumonic consolidation is the frequent report after inspection of such a chest film. There is a distinct foreign body type of distribution with the right side more affected than the left, the lower lung fields more than the upper, and the posterior areas more than the anterior. On close inspection these shadows may suggest the fine fibrosis and peri-bronchial thickening always present in this disease (figure 8).

Other conditions to be differentiated by roentgen-ray are Ayerza's disease, bronchiolitis fibrosa obliterans,<sup>85</sup> pneumoconiosis,<sup>27</sup> syphilis of the lungs,<sup>31</sup> and some cases of protracted disseminated hematogenous pulmonary tuberculosis. The oil tumors sometimes found in gross pathology may occa-

#### DIAGNOSTIC FEATURES OF OIL ASPIRATION PNEUMONIA CASES CHILDREN AND ADULTS WHO DIED

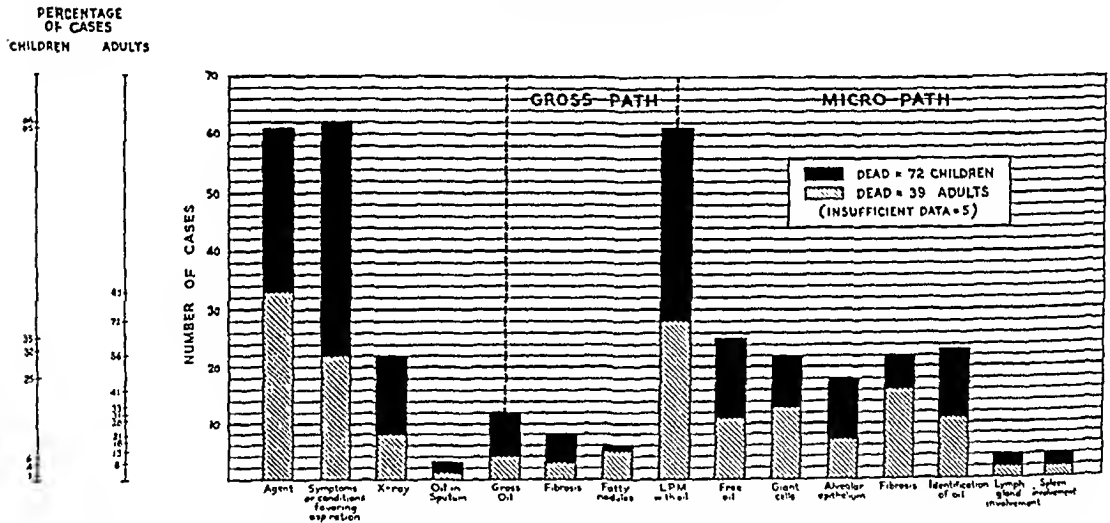


FIG. 5. Note that in the adult cases the diagnosis is based on relatively more clinical and pathological factors than in the cases of children.

sionally be identified in the roentgen-ray on retrospection but their shadows are difficult to interpret ante mortem. In the present series, the roentgen-ray picture is often complicated by the shadows produced by other pulmonary disorders.

The final important feature in the roentgen-ray diagnosis is the relative lack of change<sup>38</sup> in serial roentgen-rays, with only gradual and minor regression being observable over a period of months and years (figures 6 and 7).

#### LABORATORY AND OTHER TESTS

In the present series of cases almost every laboratory test has been made. They are incidental and non-specific. Positive findings are related to the associated disorders. The blood lipoids do not reveal any clue to the existence of this condition.

The sputum examination (centrifuged, blocked, sectioned and stained) for the presence of free oil droplets or for phagocytic cells enclosing fat droplets is of interest, should be done, but is not diagnostic by itself. Several authors<sup>47, 51</sup> have reported positive findings in this examination (figures 4 and 5). However, Quensel<sup>80</sup> in numerous normal lungs and in sputa of normal persons reports that he frequently found fat substances, free and in the alveolar epithelial cells.



FIG. 6. (Case 1.) Chest roentgen-ray upon first admission reported as showing lack of change over films taken elsewhere in May, July and September of the same year.

In one of the cases herewith reported, these findings were at first positive, but later even bronchoscopic suction failed to yield material for examination, which may indicate a change from free drainage of lipid substances earlier in the disease to the later stage where the lipoids are deposited, entrapped and fixed in the lung.

Although mention has been made of possible lessened vital capacity in this condition, no record of actual estimation has been found in the entire reviewed literature. In one of my cases in which the vital capacity estimations were made, the results were normal and approximately the same during an interval of six months.



FIG. 7. (Case 1.) Greater detail of June 1937 chest roentgen-ray at margin of involvement of the right lung showing areas of condensation and rarefaction probably corresponding to areas of oil or lipoid infiltration with normal lung tissue intervening. Note the fine fibrosis.

### CHEMISTRY

Identification of the offending agent in the lung specimen has frequently been made in this series of cases but not, however, as frequently as the opportunities would warrant. Even more frequently a non-qualified fatty substance has been identified by means of the usual fat stains. Several authors (as Pinkerton,<sup>70</sup> Ikeda,<sup>53</sup> and Fischer-Wasels<sup>31</sup>) have gone into detailed chemical study of the pathological material by the combination of stains. Ciaccio's method, solubility, iodine number, fatty acid content, and Nicol prisms (figures 4 and 5; table 4).

Quantitative estimations and differentiations of the lung-fats found have also been made, and compared with the normal fat content of normal and diseased lung, show results in quantity and quality unlike that in other known lung disease.

A detailed discussion of the fat chemistry is not the scope of this paper but it may be emphasized that it is by means of chemical analysis that final

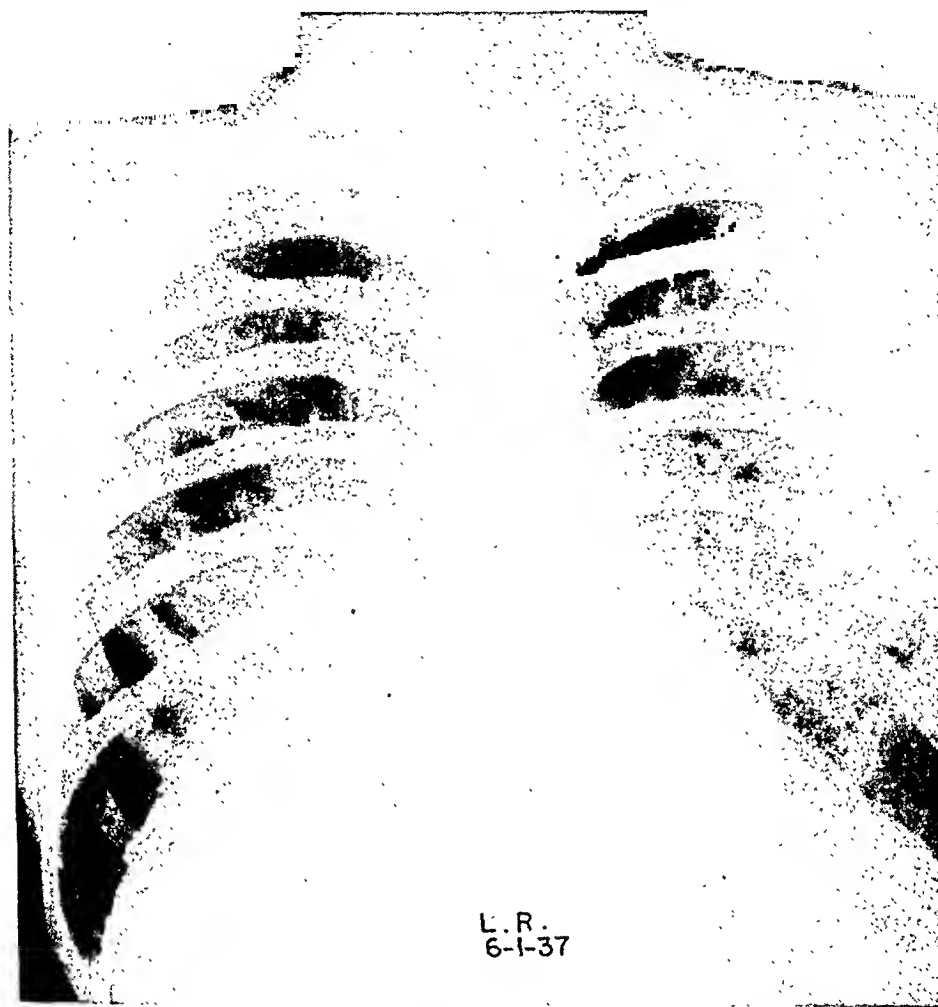


FIG. 8. (Case 1.) Chest roentgen-ray upon second admission eight months later still showing a lack of change and typical in appearance of oil aspiration pneumonia or pneumolipoidosis.

diagnostic proof is obtained and the suggestion presents itself that further chemical studies will confirm or refute the differentiation here suggested between oil aspiration pneumonia and pneumolipoidosis, exogenous and endogenous.

#### PATHOLOGY

The diagnostic findings are limited primarily to those found in the lungs and secondarily to those found in the lymphatic system, and here, mainly in the regional lymph nodes and occasionally in the spleen. If one considers

exogenous and endogenous varieties and the possibility of a faulty fat metabolism or lipoid dyscrasia, then the examination of all organs and tissues available at post mortem should be made and fully reported in the hope that findings may be correlated which will confirm or refute the existence of two clinical varieties and of a metabolic disturbance (Houck<sup>51</sup>).

The gross appearance of the lung usually presents a mixed pathological picture. The specifically involved portions appear as yellow mottled areas over the pleura. These areas may be very small and discrete or may involve one or more entire lobes of the lung, depending upon the duration and extent of the disease. On palpation these areas are firm and rubbery. On cut section of the lung gross oil is occasionally found and sometimes, as noted by several authors, has a characteristic fish odor<sup>3</sup> when the offending agent was fish liver oil. At other times gross oil is noted when the cut surface is scraped with the knife. If this is the case, scrapings may be placed on a slide and stained for fat, yielding a quick and important diagnostic finding. I should like to recommend this simple test (as done by Thomas and Jewett<sup>101</sup>) as a routine postmortem procedure.

On cut surface, the involved areas have a white, yellow, or orange-yellow appearance unlike the usual picture of pneumonia. These areas may be discrete or may gradually merge into the adjacent lung tissue. Calcification<sup>38</sup> has occasionally been noted, as has necrosis<sup>77</sup> and hemorrhage. Almost invariably, however, this pathological picture is obscured by pneumonia, atelectasis, or emphysema. It is rarely uncomplicated at autopsy.

The microscopic picture varies according to the type of offending agent involved and it is well to refer to Pinkerton's article<sup>77</sup> for a detailed description of the varieties.

The progressive lesion produced may be described briefly as follows: Free droplets of fat or oil are found in the alveolar spaces. Large mononuclear phagocytes appear which take up this substance. The droplets and the oil- or fat-laden phagocytes permeate the septal and interstitial tissues and finally enter the lymphatics. They may thus reach the regional lymph nodes<sup>51</sup> and eventually through the larger lymph channels or through alveolar capillaries they may reach the spleen through the general circulation. They may also fill the atrial spaces and extend into the bronchioles and bronchi. Concomitantly, there is a change in the alveolar epithelium which is transformed into a low cuboidal type. In the septa and interstitial tissue, progressive fibrosis takes place (figures 11 and 12). Up to this stage, the picture may well represent a pneumolipoidosis of endogenous or early exogenous nature. By this time the phagocytic activity has progressed to the state where coalescence of the individual cells has taken place to produce giant cells. The fibrosis is one of the outstanding pathological features of this disease and may progress to the extent of forming gross bands traversing the pulmonary field or even shrinking an entire lobe down to a fibrous residue (Fischer-Wasels<sup>31</sup> and Bodmer and Kallós<sup>8</sup>). Round cell infiltration is found here and there in the microscopic section, sometimes to the extent of forming

new lymph follicles, particularly along the lymph channels in the walls of alveolar capillaries and of the bronchioles, as demonstrated by Pinkerton.<sup>76</sup>

When the regional lymph nodes are invaded, they may be enlarged with very little fibrosis and small tubercle-like nodules may be visible but the lipid invasion can at best only be suspected on gross pathologic examination. Microscopically, a scattering of oil droplets is found in the periphery of the follicle and in the sinuses. Scattered through the spaces of the node may be seen macrophages with carbon and oil globules (Thomas and Jewett<sup>101, 77</sup>). When the spleen is involved,<sup>76</sup> a similar picture is found.



FIG. 9. (Case 2.) Bedside chest roentgen-ray taken 13 days before death showing what was interpreted as right lower lung pneumonia with pyopneumothorax and chronic thickened parietal pleura from base to apex. Microscopic section taken from this right lower lung area.

### PATHOGENESIS

Proof of the actual pathogenesis of the various types found in the conditions under discussion rests with the pathologists. Briefly, the following summary may be offered:

1. In oil aspiration pneumonia, with mineral oil in some form being the offending agent, there is a foreign body aspiration reaction. Mineral oil is a bland hydrocarbon.



FIG. 10. (Case 2.) Microscopic section from right lung showing the typical oil drop deposit in the alveoli and in the septa. Note also the round cell infiltration and fibrosis. No giant cells were found in this slide.

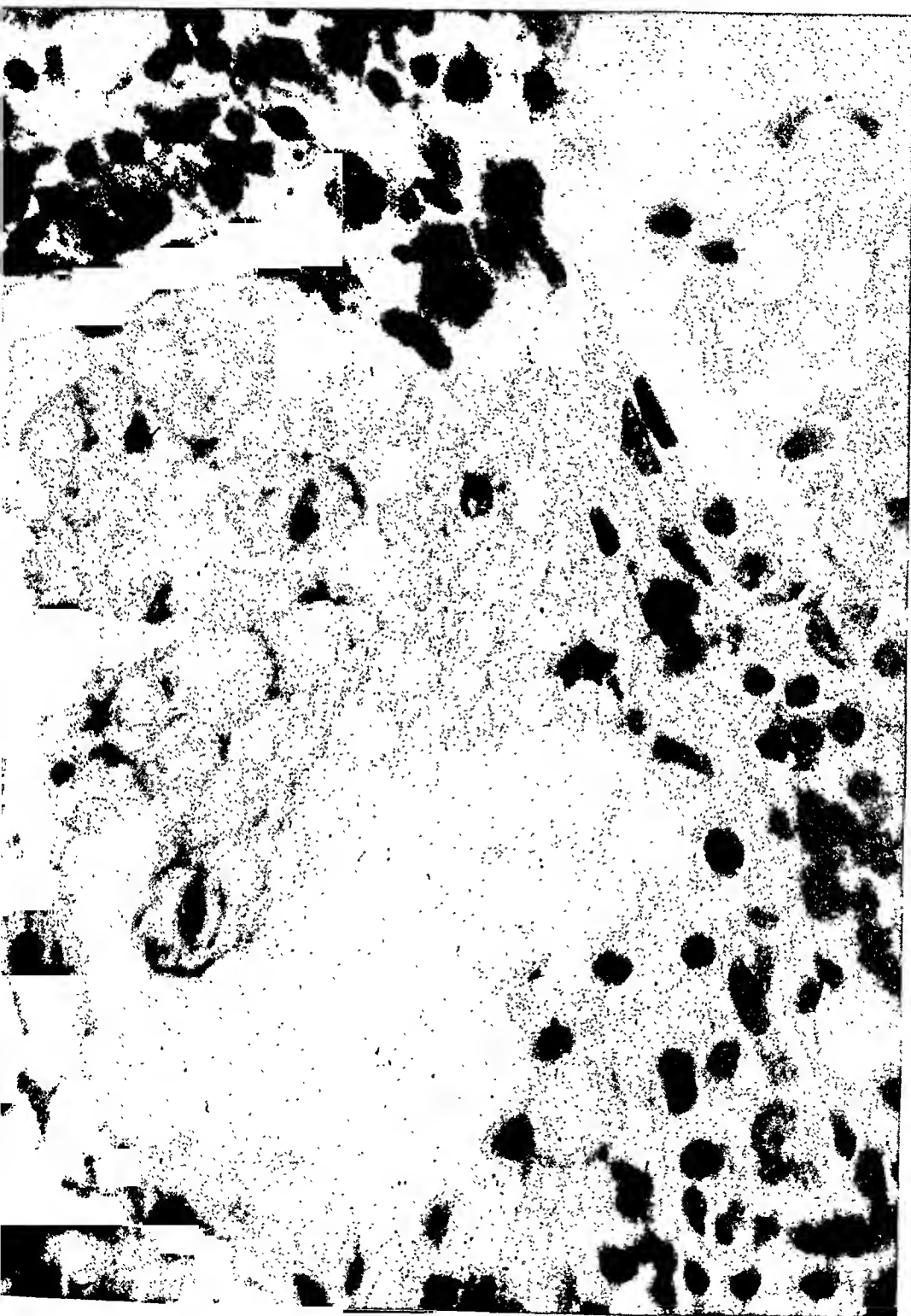


FIG. 11. (Case 2.) Higher magnification of figure 10, showing free oil droplets and oil-laden phagocytes in the alveolar spaces and also in the septal tissues. In some cases the nucleus has been pushed to one side and is crescent shaped giving the oil-laden cell a "signet ring" appearance. Here and there are seen the large mononuclear macrophages that have not as yet taken up the oil, one at the edge of the alveolar lining and another in the right field of the septum separating the two alveoli. Note the low cuboidal alveolar lining cells. The oil stained positively with Scharlach R.



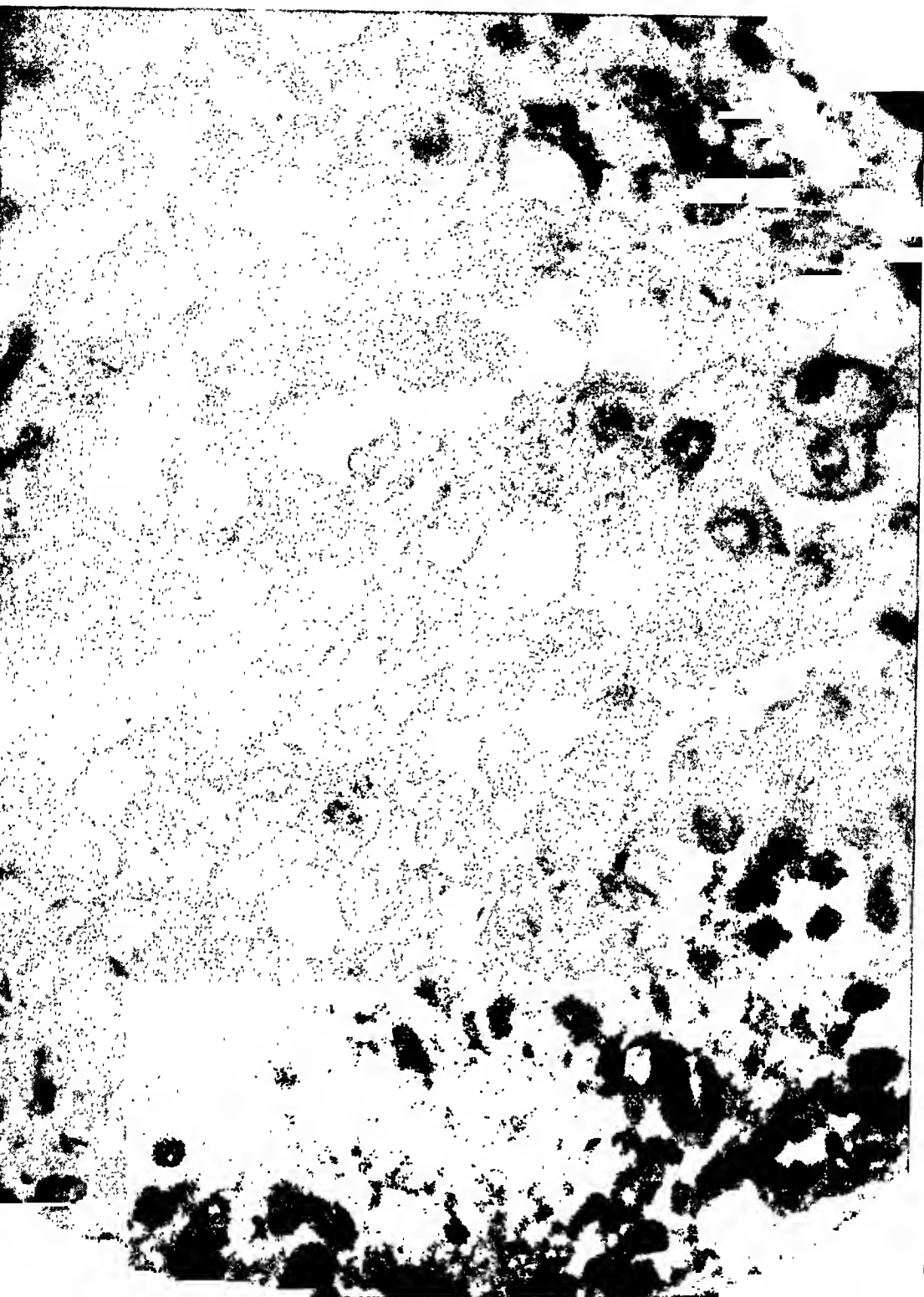


FIG. 12. (Case 3.) Microscopic section shows fat droplets and large mononuclear macrophages some of which are filled with the lipid. A few "signet ring" cells will be not d. This section stained positively with Scharlach R.

It distributes itself finely dispersed. When placed in the mouth, pharynx, trachea or nose, the opportunity for insidious aspiration under conditions favoring this accident readily occurs. Usually no harm is done because respiratory movements, ciliary actions, and reflexes leading to coughing and clearing of the throat, rid the respiratory channels of the oil. However, in the absence or diminution of these defensive mechanisms the oil may reach and fill the alveoli and in so doing may produce a pneumonic process by:

- a. Carrying infection down into the finer lung structures<sup>65</sup>;
- b. Blocking bronchial drainage and trapping oil and bacteria;
- c. Lowering local resistance to bacteria (by devitalizing the cells).

In surviving cases, there is a gradual resolution of the pneumonic process with a stationary, residual fibrosis. There is perhaps a partial removal of oil by resumption of bronchial drainage in small amounts taking place over a period of time—and by migration of the oil phagocytes into the lymphatic channels.

2. In pneumolipoidosis of exogenous nature, the processes are probably similar except that here, in addition, hydrolysis and absorption take place, furthering the clearing of the lesion, leaving a residual fibrosis as in the oil cases. In addition the pulmonary damage done may be partly caused by the action of bacterial lipase on the offending lipid. (Suggested by Pinkerton.)

3. In pneumolipoidosis of endogenous nature, the fat deposition and accumulation in the lung depend on the underlying cause, which is in some instances partly known—as in:

- a. Certain alveolar exudates of long standing (from cell degeneration in chronic pneumonic or suppurative pulmonary conditions). (Compare with Permar<sup>73</sup>);
- b. Certain types of hepato-splenomegalic disorders: Gaucher, Nieman-Picks, etc.; or, in the special form of splenomegaly and lipid-histiocytosis reported by Bloom<sup>6</sup> (cited by Pinkerton), with foam cells found in the lung, spleen, thymus and other organs;
- c. The pulmonary manifestations of Hand Schüller-Christian disease, reported by Rowland,<sup>89</sup> and Sundelius<sup>99</sup> (of 63 cases, 14 showed pulmonary involvement—22 per cent);
- d. Certain cases of lipemia (Houck<sup>51</sup>).

The pneumolipoidosis of endogenous nature may ultimately be found to be: (1) Different manifestations on the basis of an underlying systemic lipid dyscrasia; or, (2) Different clinical entities on the basis of an imbalance of oxidase and lipase cell metabolism.

## PHAGOCYTES

The origin of the large mononuclear phagocyte is still under discussion. An endothelial origin (from blood and lymph vessel lining cells) is favored by Mallory,<sup>68</sup> Permar,<sup>73</sup> and Haythorn.<sup>48</sup> Briscoe,<sup>11</sup> Sewell,<sup>94</sup> Guieysse-Pellissier,<sup>42</sup> and Fauré-Fremiet<sup>28</sup> favor the opinion that these cells are derived from alveolar lining cells (of mesenchymal origin). A third group, MacCallum,<sup>97</sup> Delafield and Prudden<sup>23</sup> believe that cells of both origins occur. Pinkerton<sup>78</sup> believes that the alveolar phagocytes are macrophages of the same origin as macrophages in other organs; that they are specialized endothelial cells, histiocytes and blood monocytes. They do not come from ordinary vascular endothelium. Westhues,<sup>106</sup> in an admirable paper report-

ing his experiments, concludes that both endothelial and alveolar lining cells, and to some extent histiocytes, are the original cells from which are derived the large mononuclear phagocytes found in the lung.

### PROPHYLAXIS AND TREATMENT

These headings are purposely grouped together as it may be justifiably stated that the best therapy is prevention. Bearing in mind the vast opportunity for insidious aspiration of oil or lipoids through the life of a civilized man, the relative rarity of the disease is apparent. Rather than to condemn or ban the use of oil or lipid agent medication or to limit food intake to that of low fat content—both tasks that are practically speaking impossible—it becomes the duty of every doctor to impress upon his patients that care and common sense should be practiced in the use and in the method of administration of oil and lipoids.

As most doctors will have found upon inquiry, no harm is done provided the patient is in good general condition and provided self-administration is carried out under correct instructions or medical supervision.

When an agent is prescribed, the following suggestions are of value:

1. The agent preferably should not be administered before retiring. The material may trickle down into the trachea and bronchi and insidious aspiration may occur in this fashion during sleep.

2. When the patient is confined to bed, flat on his back, utmost caution should be exercised in the amount, frequency, and duration of administration.

3. In cases of subdued or absent reflexes from whatever cause, substitution therapy should be used and oil and lipid agents abolished. They should be abandoned during the presence of symptoms favoring aspiration. This is particularly true in severe debilitating diseases and those conditions affecting the normal reflexes of the throat and of deglutition.

4. In suspected cases of pneumolipoidosis, iodized oil for bronchographic purposes should be deferred as a process that may add insult to injury in spite of the fact that the vegetable oil base in iodized oils is relatively harmless.

5. In infants with conditions favoring aspiration it is best to use fat free formulas.

There is no specific treatment known. The main therapy consists of adequately treating the associated disease or disorder. If the diagnosis is suspected early, during the period of administration, perhaps discontinuance of the agent and postural drainage may be beneficial—at least as a preventive measure. At a later stage, by the nature of the disease, postural drainage is a useless procedure.

Bronchoscopy as a therapeutic measure is of little value. In the early cases, there may be free drainage; in the later stages the lesion is beyond the reach of the bronchoscope.

Radio-therapy has been used in several cases but this should rather be warned against as it may augment existing fibrosis.

Activity should be reduced to conform to the disability resulting from the pulmonary involvement. Passive respiratory exercises may perhaps be tried. The more strenuous forms (blow bottles) are best avoided as ineffectual with regard to the fibrosis and are probably further debilitating in producing or increasing emphysema and possibly leading to right heart strain or failure.

So much for pneumolipoidosis of exogenous nature. Rational therapy of pneumolipoidosis of endogenous nature, except when the underlying cause may be known, must await further development by biochemists and pathologists of knowledge of lipid metabolism that may indicate the pathogenesis of the disease entities in this group.

### PROGNOSIS

The usual cause of death is the accompanying disease or disorder. The prognosis in an uncomplicated case is usually good, leaving the patient with a varying degree of pulmonary fibrosis and with a corresponding limitation in his activities, but not such usually as to preclude the average normal activity.

### CASE REPORTS

*Case 1.* A white man, aged 40, bank employee. First admitted to St. Luke's Hospital September 1936. Onset of the present illness dates back to 1928 when patient began to receive treatments for sinusitis. Had been using a paraffin oil base spray at least three times a day, one application always at night before retiring. This procedure was followed over a period of eight years.

In the same year, 1928, he had several operations with removal of turbinates and sub-mucous resection in addition to treatments and irrigations of ethmoidal, sphenoidal and antral sinuses.

He was in general good health except for three or four sinus flare-ups during the year, accompanied by fever up to 102° F., lasting three to seven days. He was conscious of occasional post-nasal drip. He was able to attend to business regularly with the exception of the few days during these acute flare-ups.

In May 1935 the patient was aware of fatigue, suffered some loss of weight (4 or 5 pounds) and felt generally run down.

In January 1936 he had what he thought was another sinus flare-up. It started with a "grippy" feeling which progressed into prostration with chills and fever up to 105° F. The sinus irrigations were clear at this time. Dr. Adams at Katonah, N. Y., believed the patient had pneumonia or a bronchopneumonia of an unusual type inasmuch as he had no cough, expectoration, hemoptysis, chest pain, dyspnea or palpitation. With no sputum available, a pneumococcus typing was not done. There was a numerical variation in leukocytes that was not diagnostic.

The patient recovered in 26 days but felt too tired to resume work until May 1936. He worked for a few days and then began to run a low-grade fever again, 101° F., which continued for about a week with occasional nausea, vomiting and exacerbation of sinusitis. He failed to gain and now noted dyspnea after moderate exertion.

Dr. Adams at this time (September 1936) suspected an oil aspiration pneumonia and referred the patient to the Medical Service of Dr. Lewis F. Frissell at St. Luke's Hospital. Roentgen-rays taken in May, July and September of this year were briefly interpreted as unresolved lesions of the lung with little change noted in the series of pictures.

On admission to the Hospital the patient was a well-developed and well-nourished man and did not appear acutely or chronically ill. The positive findings on physical examination were: Temperature 99° F.; weight 138; diminished resonance below the ninth rib posteriorly on the left, with fine moist râles at the posterior left base and in the left axilla to the anterior axillary line. Breath sounds and voice were normal. There was a slight diminution of resonance below the right clavicle; blood pressure was 120 systolic and 70 diastolic and pulse 88. There was a slight dorsal scoliosis; moderate sized hemorrhoids were found.

*Nose and Throat Consultation:* Left middle turbinate removed; right middle turbinate partly removed; ethmoidal and sphenoidal sinuses were clean; on irrigation, both antra gave clear returns; tonsillar re-growths in both fossae; rest of the examination negative.

*Roentgen-Ray Examination:* The chest plate showed the heart, aorta and diaphragm to be normal. The left lung field revealed consolidation involving the lower half of the lung. On the right there was a consolidation extending from the lower pole of the right hilum down to the diaphragm and out almost to the periphery. Compared with the former films, the right sided lesion appears stationary; the left, however, more extensive. (Figures 6 and 7.) Roentgen-ray of the sinuses showed chronic mucosal thickenings of both antra. The other sinuses were clear. Electrocardiogram showed a relatively normal tracing. Vital capacity was 81.4 per cent (September 1936). Other laboratory findings were essentially negative.

Urine negative; Wassermann and Kline tests negative; urea N 14.7 mg. per cent; sugar 100 mg. per cent; CO<sub>2</sub> 51.9 volumes per cent; stool negative; malaria-hunt negative; hemoglobin 100 per cent; red blood cells 5,000,000. The leukocytes were 7,800 with 68 per cent polymorphonuclears; 28 per cent lymphocytes; 4 per cent transitionals. The count rose to 13,000 with a subsequent drop to 10,000 without increase in the polymorphonuclears. Sputum was negative for tubercle bacilli on three occasions. Free oil droplets were found in the sputum examination twice on consecutive days although no cellular elements were found. The patient had no expectoration so these specimens were obtained by clearing the throat in the morning on arising.

*Treatment:* The patient was on bed rest with a regular diet. Until the oil droplets were found in the sputum he received four nightly doses of mineral oil (oz. 1). He had no complaints and slept well and was discharged from the hospital in October 1936, after 11 days.

He returned under the care of Dr. Adams with occasional visits to Dr. Forbes of New York, for checks on his sinus condition; Dr. Forbes also made a bronchoscopic examination without any positive findings. Nothing was seen from which a biopsy specimen could be obtained. No abnormal secretions were found. The bronchi were patent and normal in appearance. A suction specimen from the lower bronchi revealed no visible fat droplets.

Upon recommendation the patient went to Arizona for four months. There were no constitutional or respiratory symptoms during this period except for the following: Weakness and fatigue, mild dyspnea on moderate exertion, pulse elevation to 126, occasional low-grade fever 99° F. to 99.2° F., elevation of blood pressure to 140 systolic and 90 diastolic; weight remained stationary. The vital capacity was now 79 per cent six months after the first estimation was done. Examination of the lungs revealed dullness at the left base extending to the left axilla with harsh and loud breath sounds and prolonged expiration. There were numerous medium to fine moist râles. On the right side there were occasional moist râles in the axilla and at the

level of the scapular angle. Roentgen-ray examinations remained unchanged. A bronchogram with iodized oil was suggested to rule out the possibility of bronchiectasis but was not done.

Upon return (June 1937), the patient submitted to hospitalization at St. Luke's Hospital for a check-up. He still complained of lassitude, fatigue and mild dyspnea on exertion. He was afebrile, had a normal pulse rate, and except for a moderate elevation of the white blood cells, the blood picture was normal and the blood chemistry unchanged. Sedimentation rate at this time was 19 mm. in one hour and the blood cholesterol was 222. Sputum was not produced spontaneously but a five day specimen collected by forced morning cough was negative for fats by stain, and a section made from blocked concentrated sputum sediment showed only a small amount of debris but nothing that would take the fat stain. Postural drainage produced no bronchial elimination. The gastric contents concentrated for tubercle bacilli were negative. A chest roentgen-ray taken at this time, June 1937 (figure 8), showed no change. Since the last discharge, June 8, 1937, the patient has remained at home. When last heard from, May 1938, he was still complaining of lassitude, fatigability and dyspnea on mild exertion.

This case is reported as representative of oil aspiration pneumonia in a living adult.

*Case 2.* This is a white man (Jewish), aged 60, storekeeper. Admitted to the Neurological Service of Dr. R. G. MacRobert and transferred to the Chest Service of Dr. G. Thorburn at Lennox Hill Hospital in September 1936. Onset of the present illness dates back to 1925, when the patient had a sudden loss of consciousness and a left hemiplegia. There was gradual improvement and the patient was soon able to walk about. In 1931 the patient found he was unable to talk and had difficulty in swallowing. He was unable to protrude his tongue and noticed inequality of facial musculature. There was again gradual improvement. The patient had a fear of being alone and of entering subways. At one period, dysphagia was such that he had to be fed through a stomach tube. He showed a gradual loss of weight. Four weeks prior to demise the patient had a slight cold which incapacitated him totally. He grew very weak and, although he tried to cough, was unable to expectorate. He ran a continuous elevation of temperature. He felt more comfortable in the orthopneic position. With his cough and fever, he also had headaches, vertigo, occasional vomiting and fainting spells.

Checking the history, the following information was obtained from the widow in March 1938: The patient had been very constipated for the 11 years preceding his death and over this period of time took one tablespoonful of mineral oil every night, using thus many quarts of it as a laxative. At times, this medication was alternated with other laxatives, cascara, milk of magnesia, pills, etc., up to two weeks before death. He had never used nose drops or sprays. The patient's history included the usual childhood diseases (measles, mumps, whooping cough, colds, tonsillitis), and he always had had a slight non-productive cough. He had urgency and frequency of urination.

On physical examination, the patient was thin to emaciation. The temperature was 103° F. and the pulse 100. The patient had difficulty in breathing. Examination of the chest revealed dullness at the right base, and a general scattering of mucous râles over both lungs, finer and more distant over the right base. Vocal fremitus was conserved throughout. Heart examination was unsatisfactory due to over-lying mucous râles. Blood pressure was 108 systolic and 68 diastolic. Generalized weakness with slight muscular atrophy and loss of strength was found particularly marked on the left side. Teeth were in very poor condition. He was unable to move his tongue which was found flabby to touch. Pharyngeal reflexes and palatal movements were absent. Sense of touch in the posterior pharynx was present but diminished compared with the touch sense of the buccal cavity membranes. Dysarthria was

found. The speech was stammering and stuttering. Test phrases were impossible. Equilibratory tests were well performed. The handwriting was good. The deep and superficial reflexes were present and active. Abdominal reflexes were absent. No abnormal reflexes elicited. No signs of meningeal irritation, no sensory disturbances, no disturbance of stereognosis, baragnosis or topognosis. The pupils were equal but did not react to light; the right pupil was larger than the left. Fundi showed slight arteriosclerotic changes on the right. Examination of the other cranial nerves revealed poor subjective and objective taste. Movements of the facial muscles were impaired on the left. Poor articulation of labials. Absent pharyngeal reflexes bilaterally; impaired swallowing; impaired movements of tongue with inability to protrude it. Subsequent examination of the chest revealed signs indicative of thickened pleura with or without fluid in the right chest. Fluoroscopic and roentgen-ray examination of the chest showed areas of dense triangular shadowing below the right hilum and pleural effusion with at least three fluid levels, one of these levels half way up the thorax. Generalized thickening of the pleura on the right side and patch consolidation shadows on the left lower lung field. The roentgen-ray was interpreted as a pneumonic process of the right lower lobe with possible collapse of the right lower lobe with over-lying effusion or pus and a hypostatic bronchopneumonic process on the left (figure 9). Several taps were attempted, finally producing thick, green, foul pus and tube drainage was instituted.

Laboratory examinations revealed a leukocytosis of 16,900 white cells with 96 per cent polymorphonuclears. The blood chemistry was negative (Urea N 12.7, creatinine 0.5, uric acid 2.7, and sugar 142 mg. per cent; CO<sub>2</sub> 56.7 volumes per cent). Urinalyses showed some albumin and occasional hyalin casts. The chest fluid showed no growth in anaerobic or aerobic cultures. The patient ran a septic temperature from 101° to 103° F. with a terminal rise to 105° F. The nurses' notes revealed the fact that the patient was unable to expectorate. He showed great difficulty in swallowing even sips of water and choked at times on ingestion. He developed a decubitus ulcer over the coccyx. No oil or lipid agent was administered during hospitalization.

The patient died October 12, 1936.

The autopsy, excluding head examination, was made the following day. The anatomical diagnoses were: Encapsulated empyema, right pleural cavity; interlobar abscess of right lung; diffuse bilateral bronchopneumonia; generalized arteriosclerosis; coronary sclerosis; dilatation of right ventricle; chronic passive congestion of liver; chronic passive congestion and fibrosis of spleen; renal arteriosclerosis; dilatation of stomach; and decubitus ulcer. Cause of death: Diffuse bilateral bronchopneumonia and arteriosclerotic cardiorenal disease.

The examination of the thorax revealed 150 c.c. of turbid yellow serofibrinous fluid in the left pleural cavity with a few pleural adhesions to the diaphragm. Section revealed yellow-gray consolidation of left lower lobe and lower half of left upper lobe. The right lung was adherent everywhere to the chest wall. Upon breaking through the adhesion a large cavity was revealed over-lying practically the entire right border of the lung. The cavity contained a moderate amount of green-yellow pus. Upon removal of the lung, a second small cavity was found; both cavities were encapsulated. The parietal pleura was greatly thickened and leathery in quality. The empyema did not perforate the parietal pleura. A third abscess about 3 cm. in diameter was located between the upper and middle lobes and was separate from the empyema cavities. There was pus in the upper right bronchus. The lower and middle lobes were firm and on section revealed yellow-gray consolidation.

On microscopic examination, the following note was made: "Lungs: Congestion and infiltration with small round cells and polymorphonuclears. The lung presents a peculiar foamy appearance as if the alveoli and interstitial tissues contained a great deal of fat. (Figures 10 and 11.) When stained with Scharlach R, this is demon-

strated to be the case." (This slide was not preserved.) The liver showed moderate congestion and numerous focal areas of fatty degeneration. The spleen was interpreted as chronic splenitis with deep congestion and fibrosis. (No foam cells were seen.)

This case is reported as representing oil aspiration pneumonia with autopsy findings. The fact that no paraffinoma or giant cells nor extensive gross fibrosis were found in spite of 11 years' administration of oil may be explained on the basis of insidious aspiration of small amounts of oil over a long period. Massive accumulation may have been prevented by the cough reflex. Although the patient was unable to expectorate, he probably raised the oil to the pharynx and swallowed it. Perhaps a more likely explanation is that the aspiration of the oil took place during the shorter period (four weeks) of his last illness prior to admission to the hospital.

*Case 3.* White, male infant, eight days old, admitted to St. Luke's Hospital, Pediatric Service of Dr. Elmer F. Johnson because the parents noted symptoms similar to those of a brother, five months of age, who had died one year previously with amyotonia congenita. The child had had no other illnesses, was breast-fed for two days and since then had been on bottle feeding. (Formula not stated.)

The patient showed good development and nutrition and weighed 8 lbs. 10½ ozs. It was noted that the patient had a weak cry, had jerky respirations and was lying motionless. The musculature was flabby, spine poorly supported when picked up; the fontanels were open and there were cephalo-hematomata of the parietal regions; knee jerks were not obtained and there were no plantar reflexes. A biopsy from the right gastrocnemius muscle led to the diagnosis of amyotonia congenita.

The routine laboratory examinations and skin tests were negative except for a leukocytosis of 13,300 with a relative lymphocytosis (62 per cent lymphocytes).

Subsequent examinations revealed a cretinoid appearance with a rather large tongue. Skeletal muscles were weak, particularly the spinal group, and the baby did not move the extremities; fontanels and sutures were wide open. The chest was flattened laterally with an outward flare at the base, but the lungs were clear throughout hospitalization. The child did not take feedings very well and occasionally vomited and regurgitated the evaporated milk formula. During these episodes the vomitus was apparently aspirated as the baby turned very cyanotic and stopped breathing. The foot of the bassinet was elevated in an attempt to prevent aspiration. Examination of the throat was negative so it was believed that the difficulty in swallowing was due to the general condition. The infant was afebrile during the period of hospitalization. Symptomatic treatment, regulation of feeding, and thyroid extract did not result in any improvement.

The final note reads as follows: "For the past three weeks, the baby has had jerky respirations and periods of being cyanotic and at times is gray in appearance, and has been constantly so the past three or four days. During the last 24 hours the baby vomited some of the feedings and had severe attacks of deep cyanosis and periods of cessation of breathing. He died during one of these attacks on the twenty-fourth day of hospitalization."

An autopsy was done eight hours post mortem. On opening the chest, no fluid was found in either pleural cavity. The pleural surfaces were smooth throughout. The upper and lower lobes of the right lung were non-crepitant and on section had a deep red-gray appearance. The trachea and bronchi of both sides contained coagulated milk curds. The liver was enlarged. Cut section showed no gross abnormalities. Spleen was normal and two small accessory spleens were present. Mesenteric lymph nodes about the celiac axis were enlarged and soft. No gross abnormalities were found in any of the other organs including the brain. The anatomical diagnosis was: Amyotonia congenita and bronchopneumonia, right upper and lower lobes.

Microscopic examination of the lungs showed collapse of many of the alveoli while others were filled with desquamated swollen septal cells, monocytes, blood and



serum. Other alveoli were filled with polynuclear cells in areas scattered about the vicinity of the bronchioles. Scattered through portions of the lung were areas which showed free droplets and large mononuclear cells. Many of these mononuclear cells showed fat droplets, some of them completely filled, producing the typical "signet ring" effect of fat replaced cytoplasm with peripherally placed and flattened nucleus. This section stained positively with Scharlach R (figure 12). The liver showed some congestion of the sinusoids in the region of the central veins. The medulla of the adrenal showed a dense supporting tissue with areas of fatty degeneration. The anterior and posterior columns of the spinal cord in the cervical, thoracic, and lumbar regions revealed a paucity of ganglion cells which, however, appeared normal in architecture. Muscle sections revealed minute muscle cells perfect in structure but diminished in size, alternating with normal or slightly hypertrophied cells.

Microscopic diagnosis: Amyotonia congenita; bronchopneumonia.

This case is reported as representative of pneumolipoidosis of exogenous nature.

*Case 4.* Male infant, 23 months old, white, admitted to St. Luke's Hospital August 27, 1934, to the Pediatric Service of Dr. F. Elmer Johnson, with a history of moderate fever for five days.

The child was listless and apathetic and had vomited on one occasion only. One dose of castor oil had been given for constipation at the onset of the illness five days before. The baby took all its feeding poorly.

The past history revealed that the baby had cod liver oil at the age of three months. The amount and the duration were not stated but it was stopped because of vomiting.

On examination the baby appeared acutely ill and was very irritable. Shallow respirations and occasional cough were noted.

Examination of the chest revealed dullness, broncho-vesicular breath sounds and a moderate number of moist râles over the right lower chest. There were slight rosary nodes in the ribs.

Röntgen-ray examination revealed consolidation of the lower outer two-thirds of the right upper lobe which on subsequent examination extended through the whole right upper lobe and right middle lobe (figures 13 and 14). During his stay in the hospital the baby became more apathetic, listless and exhausted. There was a low-grade fever, from 98° F. to 101° F., with a disproportionately high pulse rate. Bilateral otitis media developed necessitating myringotomies. From the varying physical signs the clinical impressions were listed as bronchial pneumonia, localized pneumothorax, right lung abscess and fibrotic lung. Neurological signs developed which at the time led to consideration of a brain abscess, frontal lobe involvement. The child was fed by Levine tube for 16 days. However, he was fed fluids without milk or other fat substances and later on 50 per cent protein milk alternating with liver juice. Only once was mineral oil  $\frac{1}{2}$  oz. given through the tube.

The nurses' notes state that the Levine tube and the feedings through it were taken rather well without vigorous effort to remove it. The child was variously described in the nurses' notes as being irritable, nervous, toxic, coughing, and, without the Levine tube, would present a definite feeding problem. Fluids were poorly taken due to restlessness, crying or coughing, or else were refused entirely or taken only with forcing. The stomach was lavaged every three hours prior to feeding. The child gradually lost ground and died on the thirty-first day of hospitalization with a terminal temperature of 103° F. and a pulse rate of 156.

The autopsy was performed within 12 hours of death. The body was definitely undernourished but well developed. There were no palpable lymph glands. The right lung was heavy, 175 grams, and adherent to the diaphragm and to the posterior lateral chest wall.

On section of the right lung numerous cavities from 0.5 to 1.5 cm. were found containing thick creamy purulent fluid. The confluent areas consisted of saccular

dilatations of the small bronchi whose walls were fibrous and non-collapsible. The surrounding lung was closely packed with confluent, pale, firm, consolidated granular areas and bronchopneumonic infiltration. The left lung weighed 75 grams, was moderately congested and showed a fresh infarct 1 cm. in diameter. The liver was markedly enlarged (600 grams), pink, soft, with a very greasy cut surface. The spleen was soft, edematous and slightly congested and showed distinct lymphoid markings. There was slight hypertrophy of Peyer's patches and the mesenteric nodes were enlarged, soft and slightly congested.

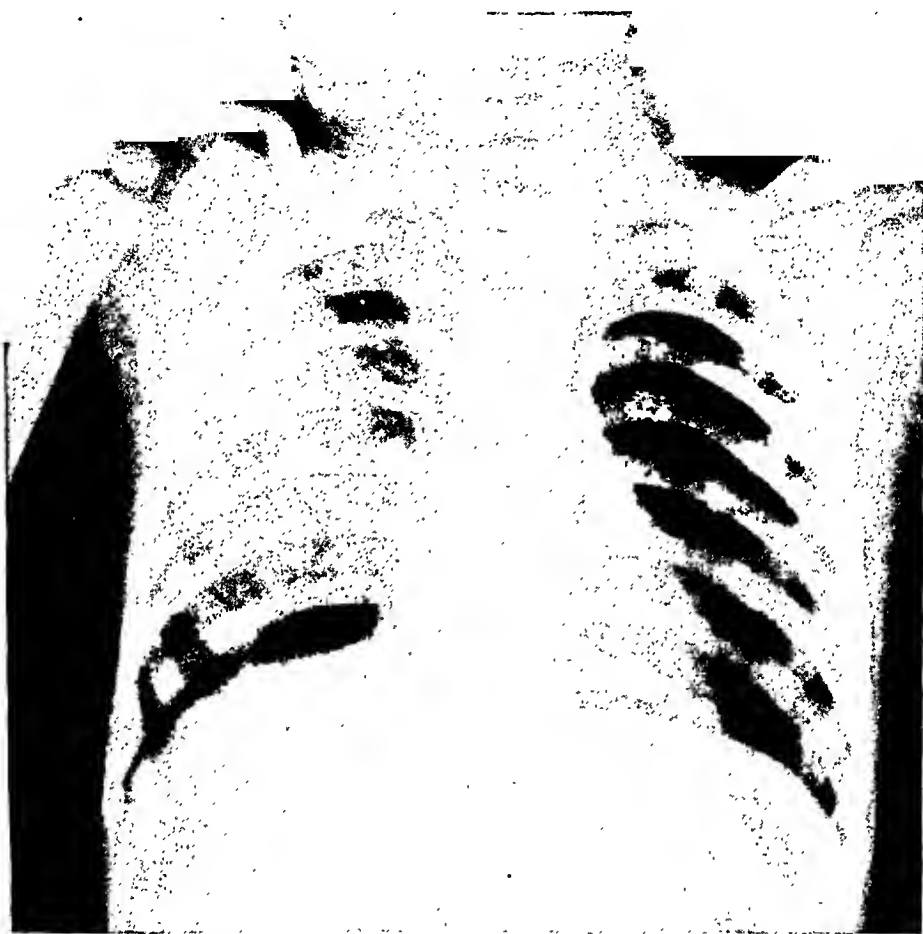


FIG. 13. (Case 4.) Chest roentgen-ray of case reported for discussion taken on day of admission showing a maximum pneumonic involvement of the lower lateral portion of the right upper lobe.

Anatomical diagnosis: Right suppurative bronchiectasis with multiple abscess cavity formation; right bronchial pneumonia with pleurisy; infarct left lung; cerebral congestion and edema; fatty degeneration of the liver and healed rickets.

On microscopic examination, the section of the right lung showed large monocytes in the alveoli which stained positively with Scharlach R. Other alveoli were filled with Scharlach R stained droplets and cellular elements. Scharlach R stained fat was also found in the septa intracellularly. In some areas there was confluence of the stained droplets. Infrequently fine concentric staining was seen in parts of the capillary wall. Definite cuboidal alveolar lining epithelium was found here and there. There was much round cell infiltration, sometimes perivascularly, and at times packing

alveoli with an interspersation of Scharlach R stain. In the areas thus involved there was a fine fibrosis and a teased out appearance of the stain. No stain was found in the blood vessels, bronchioles or bronchi (figure 15).

In the follicular centers of the mesenteric lymph node a few large mononuclear cells were occasionally seen with large pale nuclei and pink cytoplasm (H. and E. stain). A rare vacuole was seen now and then only. In the liver the parenchymal cell cytoplasm was entirely replaced with large discrete droplets. The cells were filled or distended with fat (vacuolated), pushing the nucleus to the periphery and flattening it in many instances.

The other microscopic findings are omitted for the sake of brevity.



FIG. 14. (Case 4.) Roentgen-ray taken four days later showing an increased involvement of the right upper lobe and the Levine tube in situ.

This case has not been included in the above summarized series of cases but is reported separately for discussion of diagnosis. Several "diagnostic features" favoring the diagnoses under discussion are presented:

1. One-half ounce of mineral oil given during hospitalization through Levine tube.

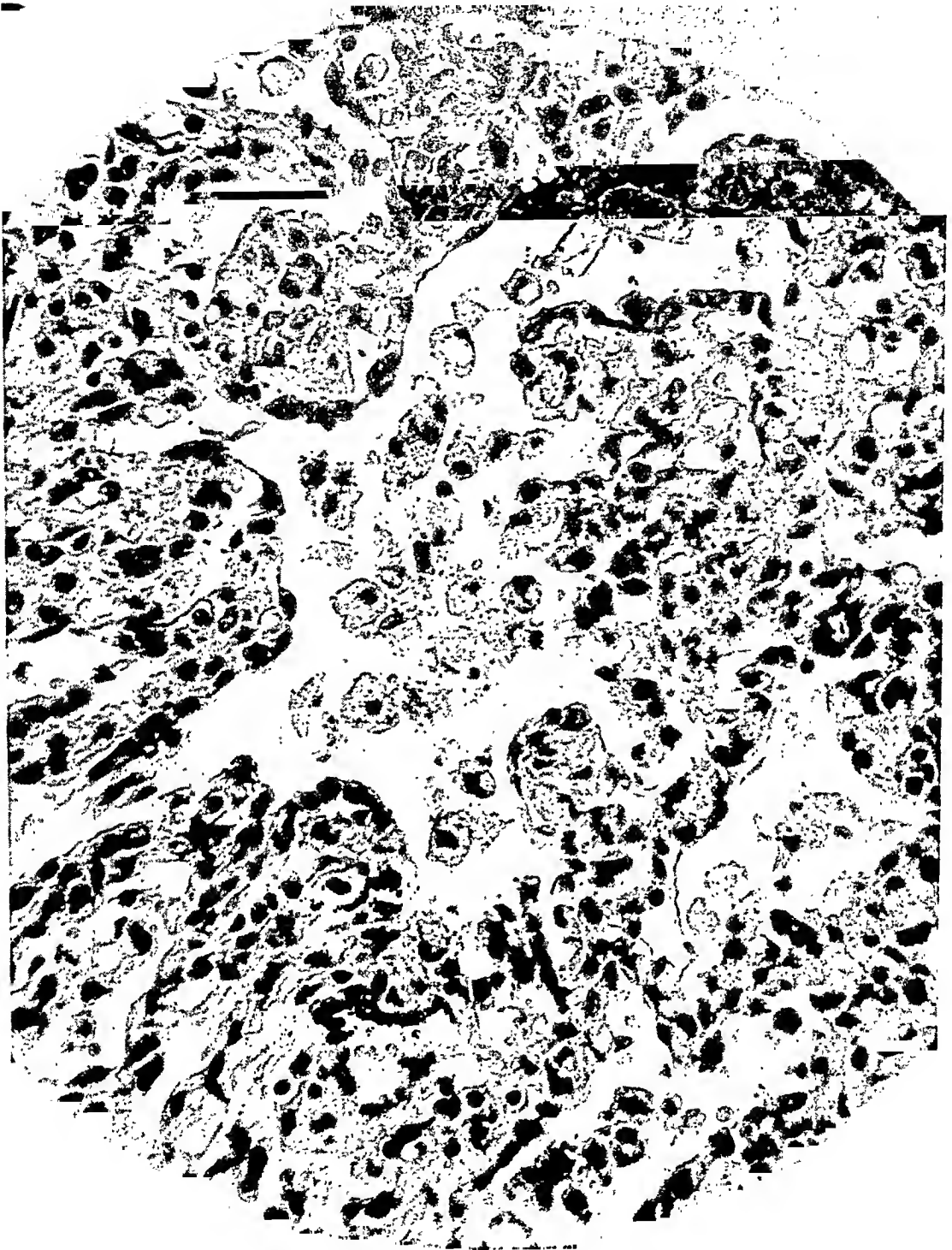


FIG. 15. (Case 4.) Microscopic section. Note large mononuclear cells in alveolar spaces. Also in the septal tissue (upper right field). Several of these mononuclear cells show vacuoles either from phagocytic activity of exogenous lipoid or from fat deposit by disturbance in oxidase lipase cell metabolism. Note also alveolar cuboidal lining epithelium. The monocytes and phagocytes here seen stain positively with Scharlach R.

2. One dose of castor oil given at onset of illness, five days before admission.
3. Cod liver oil had been given at the age of three months.

Several conditions favoring aspiration are presented: Listlessness, apathy, vomiting, irritability, cough, neurological signs, feeding difficulty, and Levine tube feeding with lavage every three hours.

Physical signs and chest roentgen-ray examinations although not "typical" do not preclude the diagnosis under discussion. The complicating otitis media and pneumonia (bronchial) are supporting diagnostic factors. The gross pathologic examination does not reveal any typical picture. The microscopic examination of the involved lung, however, does show large phagocytic monocytes some of which have enclosed fat- (or oil-) staining droplets. There is evidence of transition of alveolar lining cells to the low cuboidal type. Fibrosis is also present. On the basis of the above, it may be questioned whether this is a case of early reaction to mineral oil (oil aspiration pneumonia), or an endogenous accumulation of cell lipoids following a prolonged chronic pulmonary infection (pneumolipoidosis of endogenous nature).

### SUMMARY

#### REVIEW OF 136 CASES MENTIONED OR REPORTED IN THE LITERATURE

The terms oil aspiration pneumonia and pneumolipoidosis are suggested as covering the various phases of this clinico-pathological entity. The disorder is relatively rare in occurrence but conservatism in statistics is recommended until a larger series of fully reported cases is available. The clinical diagnosis is not based on any distinctive features but on a combination of facts:

1. A definite history of the use of an oil or lipid agent.
2. The presence of symptoms or conditions favoring aspiration, especially important where lipoids of food may be the offending agent.
3. Symptoms are mainly those of associated diseases or disorders which are most frequently found to be respiratory tract infections and other infectious diseases, central nervous system disorders, impaired general condition, and feeding or swallowing difficulties. Usually there is a combination of two or more of these disorders.
4. Physical examination reveals no specific signs. There is usually some degree of nutritional disturbance. Rapid respirations are frequently recorded. Fever, if present, is usually low-grade and the chest signs are those of the usually associated respiratory infection.
5. The roentgen-ray is of the greatest diagnostic value but may often be difficult to interpret due to other pulmonary diseases. A lack of change over a long period of time in serial chest roentgen-rays is an important point.

6. Sputum examination for free oil droplets or large phagocytic monocytes containing fat or oil should always be done in suspected cases.
7. Interval vital capacity estimations are recommended.

The gross and microscopic pathology is briefly described.

Final diagnostic proof is obtained by identification of the offending agent by chemical analysis of the oil or lipid in the involved lung tissue. It is further recommended that scrapings from the cut surface of lungs in all cases of lung examinations be streaked and stained for fat at the time of autopsy. If the above test is positive, qualitative and quantitative chemical analysis for fats should be done.

The pathogenesis of oil aspiration pneumonia and pneumolipoidosis of exogenous nature and pneumolipoidosis of endogenous nature is briefly touched upon.

The best therapy is prevention. Recommendations on prophylaxis are made. The treatment is mainly that of the associated disease or disorder.

Prognosis is dependent upon the accompanying disease or disorder. In uncomplicated cases, the prognosis is good.

Four cases are reported.

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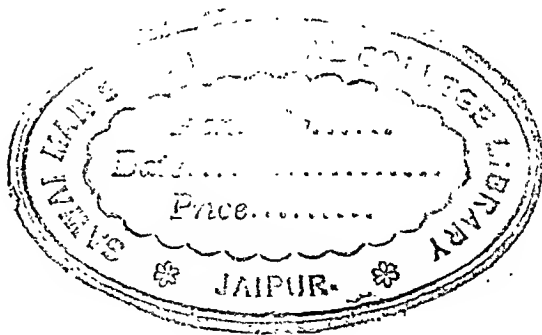
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# THE DIAGNOSIS OF POLYCYTHEMIA \*

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POLYCYTHEMIA vera is a relatively "new" disease. Although first described by Vaquez<sup>1</sup> in 1892, it did not become generally known until after the appearance of Osler's articles in 1903 and 1908.<sup>2,3</sup> Since that time, it has usually been considered a rarity; evidence for this is present in the very few references to the disease from year to year in the world's literature. Among the various hematological conditions listed in the Quarterly Cumulative Index Medicus, polycythemia ranks close to the last. Even in the last few years, with the evident great interest in the various disorders of the blood, the number of references per year for this disease is small.

The rarity of this disease may be more apparent than real. In the last nine years, at a relatively small hospital (about 200 beds), we have had the opportunity of studying at least 20 cases; in the past two years alone, 11 new cases have been seen. Since the diagnosis of polycythemia had not been suspected in several of these cases until after years of observation by many physicians, it is possible that the apparent rarity of the condition is at least in some measure due to its lack of recognition. The purpose of the present paper is to point out certain prominent symptom-complexes of the disease. At times, these may be so outstanding as to lead to an erroneous diagnosis. Analysis of our cases suggests that data leading to a correct diagnosis can usually be obtained from the history and physical examination. Careful consideration of the laboratory findings has further led to criteria for the establishment of a definite diagnosis of the condition and for differentiating the doubtful from the true case of polycythemia.

The symptoms of polycythemia are in all probability due to great overloading of the entire circulation with blood with resultant sensations referable to the head, the cardio-vascular system, the gastrointestinal tract, and the extremities. In some cases, a great multiplicity of symptoms is present with the result that neurasthenia may be diagnosed; in most cases, however, emphasis is placed by the patient on one bodily system or another.<sup>4</sup> In these, such diagnoses as migraine, brain tumor, and peripheral vascular disease may be made. In the following case reports, emphasis is placed upon the great differences in symptomatology from case to case.

*A. Cases with "Peripheral Vascular Disease" Outstanding.* In these three cases, the outstanding feature for two to six years was a marked disorder of peripheral blood vessels. It is possible, to be sure, that the vascular

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disorder bore no relationship whatever to the polycythemic state or that a "primary" disorder such as thromboangiitis obliterans might secondarily result in polycythemia through the development of vascular changes in the marrow (Reznikoff et al.<sup>5</sup>). This might conceivably have been the state of affairs in the first case of this group (Maurice G.). In the second case (Nathan W.) the lack of large vessel involvement, and the extremely high platelet count in the presence of relatively slight elevation in the red cell count suggest the possibility of "platelet polycythemia" or "thrombophilia" with multiple small peripheral vascular thromboses.<sup>6</sup> In the third case (Dora P.) the diagnosis of erythromelalgia was entertained for years. Since the sensations of pain, warmth, and tingling of the legs are common to both polycythemia and the rather poorly defined disorder of erythromelalgia, the possibility of polycythemia should be suspected when the diagnosis of erythromelalgia is made. In any event, symptoms of peripheral vascular disease are common in polycythemia.<sup>7</sup>

*Case 1.* Maurice G., a 40 year old Russian-Jewish canary peddler, first entered the hospital on August 10, 1928 with mild left hemiplegia. In 1927 he had developed cramps in the right leg and a sensation of coldness in the right big toe. He soon noticed increasing difficulty in walking because of claudication in the right leg. At another hospital in August 1927 the distal half of the right big toe was found to be reddish blue and very tender to touch. The diagnosis of thromboangiitis obliterans was made and lumbar sympathectomy of the first, second, third, and fourth ganglia was performed with some relief. The red cell count at this time was recorded as 5.24 million. In August 1928 he noticed tingling sensations and jerky motions of the left arm and leg and in a few days developed paralysis of these extremities. At the Beth Israel Hospital at this time, the diagnoses of thrombophlebitis of the right leg and cerebral thrombosis with left hemiplegia were made. Because of the findings of splenomegaly and a slightly elevated erythrocyte count (hemoglobin 106; red blood cells 5.42 to 6.79 million) the possibility of polycythemia was considered. In November 1929, he complained of pain in the epigastrium radiating to the sternal region and down the left arm. It was felt that he was suffering from coronary thrombosis. At this time, the hemoglobin concentration was greater than 100 per cent, erythrocytes varied from 7.54 to 10.0 million, and the blood-platelet count was close to 1.0 million per cu. mm. In June 1930 the complaints of vertigo and headache were outstanding. The patient was now plethoric with reddish cyanosis of the lips; the tongue large and thickly coated; the mucous membranes congested; the liver edge felt four fingers' breadth, the splenic edge three fingers' breadth below their respective costal margins; and the erythrocytes elevated between 7.20 and 9.70 million per cu. mm. The urine showed a very slight to a slight trace of albumin. In 1932 the red cell count was consistently in the neighborhood of 10.0 million. Treatment with occasional venesections, spleen extract, Fowler's solution, roentgen-radiation of the bones, and phenylhydrazine were all tried at various times but without much relief. Finally, he refused to take medication and insisted on occasional venesections which gave temporary symptomatic relief. In 1933, 1934, and 1935 he had frequent spells of vomiting. In April 1935 severe hematemesis occurred, following which the erythrocyte count dropped from over 8.0 million to 4.2 million. A large gastric ulcer was found by roentgen-ray. For several months after this episode, and while on a Sippy regime, he showed a reduction in hemoglobin and an erythrocyte count between 5.0 and 5.5 million. The ob-

TABLE I  
Analysis of Symptoms

	1 M.G.	2 N.W.	3 D.P.	4 S.S.	5 R.W.	6 J.G.	7 R.S.	8 G.F.	9 S.W.	10 F.R.	11 S.M.	12 C.B.	13 M.C.	14 G.M.	15 M.F.	16 R.G.	17 F.S.	18 M.A.	19 H.A.	20 S.C.
Headache	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Migraine			X								X	X								
Vertigo	X	X	X	X	X	X	X	X			X		X		X	X	X		X	
Visual (especially colored scotomata)						X							X			X	X	X	X	X (Conjunctival) nodules
Cardiorespiratory			X	X	X	X		X				X				X		X		
Abdominal pain	X					X			X	X	X	X	X		X			X	X	
Constipation	X	X	X	X		X		X	X	X	X	X	X			X	X		X	
Ulcer	X								X				X					X		
Paresthesias	X	X	X	X		X		X				X		X	X	X	X		X	
Extremities	X	X	X	X										X	X			X		
Bleeding tendency	X		X					X		X	X	X					X		X	
Thromboses	X	X	X	X	X	X		X				X						X		
Weakness	X		X	X		X										X	X	X	X	

TABLE II

## Signs

Plethoric appearance.....	Every case				
Distended retinal veins.....	Every case				
Large, geographic tongue.....	1, 3, 6, 8, 11, 12, 13, 17, 19, 20				
Congested buccal mucous membranes....	Every case				
Hepatomegaly.....	1, 2, 3, 4, 6, 8, 11, 12, 13, 14, 15, 16, 17, 18, 19				
Splenomegaly.....	1, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 16, 18, 19, 20				
Vascular disturbances of the extremities..	1, 2, 3, 4, 11, 18				
Blood pressure.....	1	2	3	4	5
	122/80	130/85	170/100	180/120 215/120	230/140
	6	7	8	9	10
	170/80	136/90	126/84	140/88	120/85
	11	12	13	14	15
	130/80	150/80	130/104	170/110	130/90
	16	17	18	19	20
	200/100	200/100	150/90	148/100	165/110

servations in this case following this severe hemorrhage were the basis for our use of the iron-deficiency regimen in the treatment of polycythemia.\*

*Case 2.* Nathan W., a Russian born Jewish waiter, aged 45, came to the Medical Clinic of the Out-Patient Department on March 30, 1935, complaining of pain and blueness of the toes of both feet. Three years previously he had been examined at another hospital for pain and discoloration of the second toe of the right foot. The diagnosis of thromboangiitis obliterans was made and there was slow improvement with Buerger's exercises. In 1933, there was return of pain, burning, and cyanosis of several toes of the right foot with beginning gangrene of the third toe. He was treated with continuous dry heat and there was again gradual improvement. He managed to continue at work until February 1935 when the symptoms of pain and burning returned in the second toes of both feet and therapy with the Pavex boot was recommended. Examination in the out-patient department showed a plethoric man with a barrel-shaped chest. The liver edge was felt two fingers' breadth below the right costal margin; the spleen could not be felt. The distal halves of both feet showed red, blue, and violet discoloration with very slow blanching when the legs were raised. The dorsalis pedis and posterior tibial arteries of both feet were readily palpable. The blood pressure was 130 systolic and 85 diastolic. Routine laboratory data showed hemoglobin (Tallqvist) 85 per cent, and a negative urine examination. The diagnosis of thromboangiitis obliterans was made and the patient referred to the wards in April 1935 for further study and treatment.

It was concluded that he was suffering from arterial occlusion involving only the small blood vessels of the feet. The diagnosis of Buerger's disease was considered most likely, although Raynaud's disease was considered a possibility. Hematological studies showed: hemoglobin (Sahli) 115 per cent; red blood cells 7.00 million; white blood cells 18,900; and a marked increase in platelets as seen from the smear. The urine was negative. A platelet count done several days later was 2.85 million; further counts ranged from 3 to 6 million per cu. mm. (!). In view especially of the latter finding, it was felt that the primary disorder was polycythemia, the chief cellular element involved being the platelets rather than the red cells or leukocytes. The local changes in the small arteries were felt to be due to the extremely high platelet count and the consequent tendency to thrombosis together with increased viscosity of the blood incident to the elevated hemoglobin and erythrocyte counts.

Further studies confirmed these impressions: the percentage volume of the platelets (thrombocytocrit) was 3 (normal about 0.5 per cent); sternal bone marrow

\* Appendix.

biopsy showed an extreme increase in megakaryocytes (which dominated the sections); roentgen-rays of the feet failed to show calcification of the arteries; the blood volume was 10,150 c.c. (120 c.c./kg.); and striking relief in symptomatology occurred when a venesection of 500 c.c. was instituted. However, this relief was short-lived and he complained of constant burning pain of the soles of the feet. In June 1935, the fourth right toe was the site of impending gangrene, the other toes being markedly cyanotic. The erythrocyte count was now 8.65 million. As no relief of symptoms occurred with heat and two venesections, he was transferred to an institution for chronic disease. Here he was given 1 to 2 injections of 300 c.c. of 5 per cent salt solution intravenously every week for about eight weeks with such striking relief in symptoms that he was able to return to his occupation as a waiter in January 1936. He has since been followed in the Blood Clinic, and has been kept symptom-free on an iron-deficiency regimen together with the occasional use of 5 per cent hypertonic salt solution intravenously.

*Case 3.* Dora P., a 57 year old Russian-Jewish housewife, was admitted to the hospital in 1932 because of severe constant pains in the legs which had begun about five years previously. For many years she had been troubled with excruciating headaches coming in spells every one to four weeks and always associated with severe vomiting. These severe intermittent headaches which were probably "migraine" disappeared suddenly at the time of the menopause. Since then, however, she frequently complained of a dull and more constant headache. She had also suffered from vertigo, weakness, backache, and since her menopause in 1925, from hot flashes. She had been told by several physicians that her symptoms were due to "high blood pressure" and "change in life." Symptoms referable to the legs had become the dominating feature in 1928. With walking, standing, or sitting (i.e. whenever the legs were in a dependent position) there was usually an unbearable "burning" sensation worse than the associated slight pain. The burning and pain were usually worse in hot weather and with hot baths and were greatly relieved by cold bathing. She had been treated for a few years for flat feet, varicose veins, etc. without relief. On admission to the Surgical Service (private) of the hospital in 1932, the diagnosis of erythromelalgia was made. Blood examinations showed hemoglobin 85 per cent; red blood cells 5.82 million; white blood cells 15,600 with 82 per cent polymorphonuclears. Preliminary injection with novocaine of the right sural nerve caused complete relief of symptoms; this was accordingly followed by section of the same nerve. For a few months there was complete relief of burning and pain followed, however, by identical symptoms in the other leg. She continued to complain of headache, vertigo, and pain and burning in the unoperated leg, and was observed several times in the Out-Patient Department. In 1934 a red cell count was found to be 7.60 million, and she was admitted to the hospital on March 25, 1934, for study and treatment of polycythemia.

The patient presented a plethoric appearance with deeply reddened mucous membranes and lips and dilated conjunctival blood vessels. The veins of the fundi were distended; the tongue was thick, large, and heavily coated. The heart was slightly enlarged to the left but was otherwise normal. The edge of the spleen was felt about three fingers' breadth below the left costal margin. The liver could not be felt. There were marked varicosities of both legs. In the dependent position, the left (unoperated) leg became strikingly red and seemingly filled with blood. The blood pressure was 190 systolic and 100 diastolic. The urine showed no albumin or sugar and no casts were demonstrated. The blood showed hemoglobin 116 per cent; red blood cells 7.60 million; white blood cells 14,000; polymorphonuclears 84 per cent, platelets 1,350,000.

A single venesection of 500 c.c. brought the red cell count to 6.2 million. The patient was then given phenylhydrazine hydrochloride in dosage of 0.030 gm. three times daily until the red cell count dropped to 4.50 million. One month after the be-

gining of treatment the pains in the legs had almost entirely disappeared. She was now able to walk without difficulty and the burning sensations had gone. There was also complete relief of headaches and vertigo. Since then, the patient has been moderately well, the chief disturbing feature being the tendency to multiple thromboses of varicose veins.

*B. Cases with "Cardiovascular Disease" Outstanding.* In the two cases which follow, the outstanding symptoms related to the heart. Was the polycythemic state the primary condition or did it follow chronic cardiovascular disease? The incidence of marked polycythemia in adult heart disease is rare, although it may not infrequently be present in right-sided heart failure associated with disease of the pulmonary artery ("Ayerza's disease").<sup>10</sup> Hypertension and left ventricular failure were present in each of the two cases described below, and it seems quite unlikely that the cardiovascular disease was the cause of the polycythemia. The increased blood volume in the disease, the increased mass of circulating blood, and the marked increase in viscosity of the blood are all important factors in increasing the work of the heart and thus in leading to premature coronary disease.<sup>11</sup> The occurrence of multiple thromboses, both arterial and venous, in polycythemia is quite frequent and is brought out particularly in Case 4.

*Case 4.* Sarah S., a Russian born Jewish housewife, aged 53, came to the Out-Patient Department in July 1929 complaining of palpitation and vertigo. In 1927 she had suddenly developed severe pain in the left lower leg accompanied by bluish discoloration. At another hospital the diagnoses of hypertension, hypertensive heart disease, generalized arteriosclerosis, and possible femoral vein thrombosis were made. At the Out-Patient Department in 1929 she stated that palpitation, vertigo, and nausea had recently become so distressing that she had taken to bed. The physical examination was stated to be essentially negative except for a blood pressure of 170 systolic and 120 diastolic. The hemoglobin (Tallqvist) was 75 per cent. The diagnoses of hypertension and neurasthenia were made. In September 1931 she was admitted to the House Service where she complained of severe headache, vertigo, palpitation, precordial pain, and frequent attacks of syncope. A week before admission the left thumb had suddenly become painful, numb, and discolored. Examination at this time showed a plethoric appearance, injected conjunctivae, congested mucous membranes, and cyanotic lips. The retinal veins were distinctly widened, and there was moderate sclerosis of the retinal arteries. The heart was enlarged (apex 14.5 cm.) and a harsh systolic murmur was present at the apex. The peripheral arteries were all perceptibly thickened and tortuous, and the blood pressure was 180 systolic and 120 diastolic. Both the liver and spleen were felt two fingers' breadth below their respective costal margins. The fingers and toes were congested and cyanotic.

The urines showed traces of albumin, the sediment being negative. The blood showed: hemoglobin 145 per cent (Sahli); red blood cells 9.41; white blood cells 8,300; polymorphonuclears 79 per cent, lymphocytes 18 per cent, monocytes 1 per cent, eosinophiles 2 per cent; platelet count 2.2 million. The blood icteric index was 17.5, coagulation time 7 to 17 minutes, bleeding time 2½ minutes, fragility test 0.44 to 0.32 of NaCl solution, hematocrit 0.76, mean corpuscular volume 80 cu. micra, blood volume 6370 c.c., plasma volume 1400 c.c. The basal metabolic rate was +9 and -6 per cent, and the gastric analysis showed from 40 to 50 units of free hydrochloric acid.

Numerous venesections were performed and then phenylhydrazine was administered until the red count remained at a level of about 5.0 million per cu. mm. The patient returned to the hospital in February 1932 complaining of generalized pains



and attacks of vertigo and syncope. The hemoglobin was now 124 per cent, and the red cell count 9.15 million. Shortly after a venesection of 500 c.c. she complained of severe pain in the chest and arms. There was an extreme drop in blood pressure and serial electrocardiograms showed the changes characteristic of coronary thrombosis. Complete heart block developed. The blood non-protein nitrogen at this time was 53 mg. per 100 c.c. No further venesections were performed. Fowler's solution in large doses gave no relief.

In October 1932 she showed the signs of cardiac decompensation; blood pressure was 210 systolic and 125 diastolic; the retinal arteries were almost occluded. In December 1932 she began to have severe attacks of dyspnea. It was difficult to control the erythrocyte count which was constantly between 8 and 9.5 million. In 1933 she died at another hospital.

*Case 5.* Rebecca W., a 64 year old Russian-Jewish housewife, was admitted to the hospital on May 18, 1934. In 1923 she complained of vague symptoms, and hypertension was discovered. In 1926 a cholecystectomy was performed at another hospital; the red cell count was normal. In 1933 she was treated for heart disease at the same hospital; the blood pressure was 230 systolic and 140 diastolic. For 10 months she had complained of orthopnea, substernal oppression, attacks of wheezing and coughing, and occasional spells of vertigo, in one of which she was unconscious for about one-half hour. Examination in May 1934 disclosed extreme bluish redness of the face, nose, ears, lips, and tongue. Ophthalmoscopic examination showed hyperemic optic discs with blurring of the disc margins. The retinal veins were greatly dilated and the arteries extremely tortuous. Flame-shaped hemorrhages were present in each eye. Crepitant râles were present at the bases of both lungs. The heart was somewhat enlarged to the left and systolic murmurs were present over the mitral and aortic areas. Although the liver could not be felt, the edge of the spleen descended three fingers' breadth beneath the left costal margin. The fingers were greatly reddened and swollen. The peripheral arteries felt moderately thickened and tortuous. The blood pressure was 200 systolic and 125 diastolic. Laboratory findings were as follows: urine, heavy trace of albumin with occasional hyaline and granular casts; hemoglobin 170 per cent (Sahli); red blood cells 11,000,000; white blood cells 12,300; hematocrit 0.76; mean corpuscular volume 70 cu. micra; blood cholesterol 384 mg. per 100 c.c.; phthalein test 40 per cent; basal metabolic rate + 38 per cent; the electrocardiogram showed coronary changes.

A venesection of 500 c.c. was done on the sixth day. Following this procedure the patient became stuporous and could not be aroused. Right hemiplegia accompanied with Cheyne-Stokes breathing soon developed. Another venesection of 500 c.c. was done on the seventh day. The temperature rose to 105° F. and the patient expired. Autopsy showed marked generalized arteriosclerosis, cardiac hypertrophy (left), coronary sclerosis, myocardial fibrosis, bronchopneumonia, chronic vascular nephritis and congestion of the kidneys, multiple renal cysts, acute duodenal ulcer, congestion of the small intestine and liver, softening of the brain (anterior left cerebrum, two areas) and one area of hemorrhage in the right cerebellum with thrombosis of the anterior cerebral artery.

*C. Cases with Symptoms Referable Chiefly to the Central Nervous System.* Symptoms referable to the central nervous system are present in almost every case of the disease. In some instances, they are outstanding, and so severe as to make the consideration of brain tumor a serious one.<sup>12</sup> Although in none of our cases were the symptoms of this degree of severity, an examination of the records of another hospital showed that in a number of cases, brain tumor was at first suspected, although the final diagnosis was

polycythemia vera. Occasionally, the differential diagnosis between the two conditions is extremely difficult since both polycythemia and intracranial neoplasm may result in lethargy, headache, vertigo, scotomata, blurring of vision, congestion of the retinal vessels and papilledema. Colored scotomata were commonly present, particularly when the red cell count was above 8.0 million.

*Case 6.* Jacob G., a 65 year old Russian-Jewish unemployed inmate of a home for the aged, began to have severe headaches in 1927. In 1931, he developed right hemiplegia and was confined to another hospital where the diagnosis of hypertension was made. In October 1932, when he came to the Out-Patient Department of this hospital, he complained chiefly of severe headache, vertigo, tinnitus, and colored scotomata, together with increasing nervousness, insomnia, and weakness. Other symptoms were dyspnea, slight precordial pain, palpitation, constipation, and paresthesias of the hands and feet. Examination at this time disclosed a plethoric appearing man. The heart was somewhat enlarged, the aortic second sound accentuated, and a rough systolic murmur was heard over the entire precordium, principally over the aortic region. The blood pressure was 190 systolic and 90 diastolic, and the peripheral arteries were greatly sclerosed. The laboratory data were as follows: hemoglobin 124 per cent; red blood cells 8.96 million; white blood cells 12,400; polymorphonuclears 84 per cent; platelets 1.24 million. With reduction of hemoglobin concentration and red cell count to approximately normal figures, there was complete subsidence of all the symptoms. These recurred with relapse to polycythemic levels and were again relieved by multiple venesections.

*Case 7.* Robert S., a 39 year old Russian-Jewish storage battery worker, was referred to the Out-Patient Department in February 1937 by his family physician who had made the presumptive diagnosis of polycythemia. The patient had noticed increasing sluggishness in the past year, and readily fell asleep at times during the day. He found it hard to concentrate on simple problems and had noticed a rather marked change in his disposition so that he became readily angered. In the past month he had developed frequent spells of dizziness and was often nauseated. On one occasion, he vomited. For a month also he had noticed frequency of urination and nocturia 5 to 6 times. Physical examination showed a very plethoric-appearing man with extremely red face, hands, and feet and congested, somewhat bluish mucous membranes. The retinal veins were greatly congested and the reflexes were hyperactive. *Neither the spleen nor liver was felt.* Involuntary twitchings of the muscles of the arms and legs were noted at times. At another visit, the spleen was just palpable. The blood pressure was 136 systolic and 90 diastolic. The laboratory data were as follows: hemoglobin 150 per cent (Sahli); red blood cells 8.0 to 8.7 million; white blood cells 12,000; hematocrit 74 to 80 per cent; platelet count 400,000 to 800,000; blood viscosity 13.4 (normal 4-5). The urine showed a trace of albumin, the sediment was negative. With the induction of an iron-deficiency regime, there was complete symptomatic relief.

*Case 8.* Gussie F., a 49 year old Austrian-Jewish housewife, was admitted to the hospital in October 1933. In 1905 she was treated for chlorosis at another hospital. Beginning in 1931, at about the time of menopause, she complained of severe hot flashes, headache, vertigo, and tinnitus. In 1932, following extraction of a tooth, she bled profusely for 36 hours; hemorrhage was finally controlled by packing. The headache and spells of vertigo became worse and were at times associated with momentary loss of memory. In 1933 she developed involuntary twitching of the fingers which would cease when attention was directed to this peculiar motion. For two years, she had visited several physicians and a variety of diagnoses had been made: menopause, neurasthenia, cerebral arteriosclerosis. Three months before admission,

she was constantly flushed and red; her lips became extremely full and dry so that she was constantly either biting or licking them. She became increasingly dyspneic and complained of palpitation and fatigue. She lost her appetite, developed severe epigastric distress and constipation and had nocturia. Two weeks before entry, she had a severe spell of vertigo lasting several hours and associated with complete amnesia. She was finally seen by a physician who, noticing her plethoric appearance, did an erythrocyte count, found it elevated, and made a tentative diagnosis of polycythemia. She was referred to the hospital on October 4, 1933, for observation and therapy. Physical examination revealed an extremely red face. The conjunctivae were deeply injected and the venules over the cheeks greatly dilated. The lips were purplish in color, the gums intensely red, the tongue large, "beefy," and deeply fissured. The retinal veins were extremely dilated. The lungs were normal. The heart showed no enlargement. A rough systolic murmur was present over the apical region. The liver and spleen were both felt three fingers' breadth below their respective costal margins. The reflexes were hyperactive but otherwise normal. A "Parkinsonian" type of tremor of the fingers was present and there was also constant licking and biting of the lips. A neurologist suggested involvement of the basal ganglia.

The laboratory data were as follows: urine, trace of albumin, no casts; blood: hemoglobin (Sahli) 118 per cent; red blood cells 10.2 million; white blood cells 10,800; platelets 2,500,000 per cu. mm.; differential count of the leukocytes: polymorphonuclears 81 per cent, lymphocytes 14 per cent, monocytes 3 per cent; eosinophiles 1 per cent, basophiles 1 per cent. Blood non-protein nitrogen was 41 mg. per cent. Basal metabolic rate was  $\pm 5$  per cent. In the second week of the patient's stay, thrombophlebitis of the veins on the inner aspect of the left thigh developed. Several venesections were performed and Fowler's solution administered, although this was later discontinued. On phenylhydrazine hydrochloride and more recently on an iron deficient regime there has been complete disappearance of all her symptoms.

*D. Cases with Gastrointestinal Symptoms Outstanding.* In common with the remainder of the body, the gastrointestinal tract shares in the general plethoric condition. Congestion in the various abdominal organs produces various types of symptoms referable to the liver, spleen, stomach, or intestines. Constant pain, apparently due to hepatic congestion, was present in Cases 11 and 12. In the first of these cases, the right-sided pain led to a diagnosis of appendicitis and the patient was operated upon; in the second case, the diagnosis of gall bladder disease was for some time entertained. Many of the patients complain of pain or a heavy sensation in the region of the spleen (Case 10). The co-existence of peptic ulcer with polycythemia has been commented upon by several observers.<sup>13</sup> In our series, peptic ulcer was found in four cases and suspected in another case. At times, the symptoms of the ulcer dominate the picture, as in Cases 9 and 13.

*Case 9.* Samuel W., a 63 year old Russian-Jewish storekeeper, was admitted on August 11, 1930, complaining of generalized abdominal cramps of four days' duration, together with vomiting and obstipation for 1 day. Prior to this illness, he had considered himself in good health. Examination showed a decidedly plethoric appearance, emphysematous lungs, greatly thickened brachial and radial arteries, blood pressure 140 systolic and 88 diastolic, and abdominal distention with spasm in the region of the umbilicus. Blood examination showed hemoglobin 130 per cent (Sahli); red blood cells 8.8 to 9.95 million; white blood cells at first 20,600, later 9,100; platelets 594,000. The urine showed a very slight to slight trace of albumin. A gastro-

intestinal series showed duodenal ulcer. The sharp attacks of abdominal pain continued and finally led to a laparotomy on September 25, 1930, at which time a perforating duodenal ulcer with peritonitis was found. A posterior gastro-enterostomy was performed, following which the patient developed massive collapse of a lung and died three days after operation. Autopsy revealed the presence of four deep, punched-out ulcers of the duodenum, adhesive peritonitis, bronchopneumonia, possible luetic aortitis, and considerable congestion of all the abdominal viscera.

*Case 10.* Frank R., a 58 year old Russian Jewish storekeeper, was admitted to the hospital on August 13, 1931, complaining of a "lump" in the left upper part of the abdomen. Although he had complained of this symptom for several years a definite diagnosis had not been made. During the eight months before admission, the lump in the left upper abdomen had grown noticeably larger and during that time he complained of a feeling of epigastric fullness after meals, constipation, gastric distress, profuse sweating, moderate itching of the skin, and slight dysuria. In the past, he had bled severely from the "tonsils" (cause unknown); from the rectum, necessitating at that time hospitalization; and from the gums upon extraction of teeth. Headaches had been present for years. Examination revealed an extremely ruddy color of the skin, and deeply congested buccal mucous membranes and pharynx. The lungs showed increased resonance (interpreted as emphysema). The heart showed moderate hypertrophy. The spleen was greatly enlarged, being palpated below the umbilical line. The liver edge was not felt. The hands, fingers, and fingernails were very florid and ruddy. The hematological findings were as follows: hemoglobin 124 per cent; red blood cells 7.36 million; white blood cells 21,300; polymorphonuclear cells 81 per cent; platelets 1.14 million; bleeding time 3 minutes; coagulation time 7 minutes. The basal metabolic rate was  $+50$  per cent. The urine showed a very slight trace to a trace of albumin.

Since the teeth were found to be extremely carious, extraction was thought advisable. Severe hemorrhage took place when a few teeth were extracted. The red cell count dropped to 4.45 million and the hemoglobin to 86 per cent (Sahli), the leukocyte count rising to 48,000. Ten teeth were extracted during three sittings, and on each occasion bleeding was profuse, requiring packing and pressure. Six days after the last extraction, the patient felt better and was discharged home.

*Case 11.* Sarah M., a 26 year old Russian-Jewish saleswoman, was admitted to the private service (surgical) of the hospital on June 13, 1932, because of recurrent pain in the right side of the abdomen. Examination showed flushing of the face and slight tenderness in the right lower quadrant. The urine was negative, the leukocyte count 14,600. Operation was performed and disclosed a hyperemic edematous appendix and a congested corpus luteum cyst of the left ovary. Appendectomy and resection of the left ovary were performed. A large hematoma of the operative wound developed with much oozing of blood into the incision. The red cell counts at this time were found to vary from 5.3 to 7.3 million, and the hemoglobin was 113 per cent (Sahli). The diagnosis of polycythemia vera was indicated. Pain in the abdomen identical to that prior to operation persisted. Almost a year later (April 1933), a roentgenologist discovered splenomegaly in the course of a gastrointestinal series. Shortly after, the following additional history was obtained. The patient had considered herself well until 1929 when she began to have severe headaches associated with scotomata, nausea, and vomiting. These were considered to be migraine, and indeed her mother had had identical headaches for many years. In 1930 a tooth was extracted; this was followed by extreme hemorrhage, finally necessitating packing. About this time she noticed persistent "redness" of the eyes; an oculist found nothing abnormal. In 1931 she noticed that her hands were red, blotchy, and cold, and apparently swollen. Her feet were also noticeably red, and frequently pained her in walking. The headaches became worse and were often associated with spells of vertigo and paresthesias of the hands, face, and tongue. A nose-and-throat spe-

cialist failed to find any abnormal sinus condition. In the early part of 1932 she began to have attacks of pain in the right side of the abdomen; these usually began in the upper quadrant and radiated downwards. At times they were associated with the severe attacks of headache and vomiting. Soon the pain became almost constant. In one bout of severe abdominal pain associated with vomiting, a physician made the diagnosis of acute appendicitis and she was operated upon, as noted above. The pain had continued and had even grown worse.

On examination in 1933 there was intense redness of the face and neck. The conjunctival blood vessels were greatly injected. The fundal veins were greatly dilated. The mucous membranes of the lips, mouth, and throat were brilliantly red. The tongue was large and well coated. The lungs and heart showed no abnormalities. The edge of the liver was felt three fingers' breadth below the right costal margin and was extremely tender. A hard spleen was felt in the comparable position on the left. The hands and feet were reddish blue, blotchy, and cold to the touch. The dorsalis pedis arteries were readily palpable. The blood pressure was 120 mm. of mercury systolic and 80 diastolic. The laboratory data were as follows: urine—no albumin, sugar, or casts; blood—hemoglobin 124 per cent (Sahli); red blood cells 7.24 million, white blood cells 9,800; differential count of the white cells: polymorphonuclears 78 per cent (21.5 per cent immature forms); lymphocytes 11.5 per cent; monocytes 2.5 per cent; eosinophiles 3.0 per cent; basophiles 5.0 per cent. Platelet count was 1,500,000 per cu. mm.

There was satisfactory response to phenylhydrazine therapy with resultant diminution, and at times cessation, of all of the above symptoms. The abdominal pain disappeared after the erythrocyte count had remained at a level of about 5.0 million for several months.

*Case 12.* Charles B., a 52 year old Russian-born Jewish merchant, was first seen in January 1935. In 1933 he began to complain of a sense of pressure in the right upper quadrant. Since this was accompanied with belching and heart burn and failure of the gall bladder to visualize with the Graham test, the diagnosis of gall bladder disease was made by his family physician and treatment with a fat-free diet instituted. When sense of pressure recurred later, he was studied at another hospital where a mass in the left upper quadrant was discovered. It was thought this might be due to an enlarged kidney, and two cystoscopic examinations were accordingly done without a definite diagnosis being made. The sense of pressure in the right upper quadrant continued, and he consulted various physicians without relief. In December 1934, while in bed, he was suddenly seized with severe pain and a vise-like sensation in the mid-chest radiating down the left arm and associated with severe dyspnea. This attack lasted for seven hours. He was in bed for two weeks. At the end of that period, routine blood counts showed hemoglobin 140 per cent (Sahli) and red cell count of 6.80 million. Additional history in June 1935 was obtained of the following: frequent very severe headaches for about four years, coming in attacks, lasting two to three days at a time, associated with blurring of vision and at times with much belching of gas and nausea. Vertigo was occasionally present. The eyes had felt "heavy" for about six months. For about a year he had noticed paresthesias of the thumb and index finger of the left hand and, for three months a peculiar creepy sensation down both arms. His hands had been as "red as a beet" for about 15 to 20 years, especially so in the summer time.

Examination disclosed the following: a plethoric appearance; congested conjunctivae; widely dilated fundal veins with normal appearing arteries; slight red cyanosis of the lips and mucous membranes; a heavily coated, normal sized tongue; a tender liver edge felt three fingers' breadth below the right costal margin and a firm spleen three fingers' breadth below the left costal margin. The heart was slightly enlarged to the left. The blood pressure was 116 systolic and 70 diastolic. There was a dusky coloration of the finger tips. The urine showed no albumin, sugar, or

casts. The blood showed: hemoglobin 128 per cent (Sahli); red blood cells 7.69 million; white blood cells 12,600; differential count: polymorphonuclears 93 per cent, lymphocytes 5 per cent, monocytes 1 per cent, eosinophiles 1 per cent; blood platelets 898,000.

The patient was given phenylhydrazine hydrochloride in dosage of 150 mg. daily with resultant diminution in erythrocyte count. When the erythrocyte count had remained in the vicinity of 5.0 million per cu. mm. for about a month, the sense of fullness in the right upper quadrant and most of the digestive disturbances disappeared. There was complete cessation of the violent headaches and visual disturbances which had been prominent before. The cardiac condition gradually improved so that the patient could continue at his business.

*Case 13.* Max C., a 44 year old Russian-Jewish laborer, came to the Out-Patient Department complaining of pain in the left upper quadrant, just to the left of the epigastrium, appearing  $\frac{3}{4}$  hr. after a meal, lasting for about 30 minutes or more, and relieved immediately by taking food. For several years he had been constipated and had complained of "gas" and sour eructations. Other symptoms were headache, frequent spells of dizziness, and colored scotomata. Physical examination showed a very plethoric appearing man, with dilatation of the superficial blood vessels of the skin of the face, the conjunctivae, and buccal mucous membranes. Small nevi of the face were present. The tongue was small, shiny, and well coated. The edge of the liver was felt one finger's breadth below the right costal margin, the splenic edge just felt. The laboratory data were as follows: hemoglobin 138 per cent (Sahli); red blood cells 8.75 million; white blood cells 18,400; polymorphonuclears 87 per cent; lymphocytes 8 per cent; monocytes 2 per cent; eosinophiles 1 per cent; basophiles 2 per cent; platelets 1.74 million; platelet volume 2 per cent; hematocrit 76 per cent. Gastric analysis—a maximum of 16 units of free HCl. Blood volume 8,900 c.c. Basal metabolic rate +10 per cent. The gastrointestinal series showed a slight irregularity at the lesser curvature of the duodenal cap, interpreted as a small duodenal ulcer. On a modified Sippy régime and multiple venesections, the patient's symptoms completely disappeared and the blood picture became normal.

*E. Cases with "Arthritis" Outstanding.* In some cases of polycythemia pains in the joints and limitation in motion make the diagnosis of chronic arthritis a definite possibility. This was the situation in two of our cases.

*Case 14.* Gertrude M., a Russian-born Jewish housewife, aged 50, came to the Out-Patient Department on June 4, 1936, complaining of vague joint pains of two years' duration. For six months, the pains had become more severe and were present in the lower back, the shoulders, knees, elbows, wrists, and finger joints. For two weeks, numbness and tingling of the fingers had been present. The diagnosis of chronic arthritis had been made by her local physician. Examination at the patient's first visit failed to reveal any abnormalities except possibly an enlarged spleen, and a definite diagnosis could not be made. A sedimentation rate was requested. Because this was found to be unusually slow, the possibility of polycythemia was considered. Hematocrit and erythrocyte determinations were respectively 0.62 and 6.16 million per cu. mm. On June 11, a large spleen and liver were discovered and the tentative diagnosis of polycythemia made. The patient was then referred to the Blood Clinic where physical examination disclosed a plethoric-appearing woman with congested conjunctival blood vessels, a large well-coated tongue, hepato- and splenomegaly (liver and spleen each two fingers' breadth below their respective costal margins), an essentially normal heart, and blood pressure of 170 systolic and 110 diastolic. The legs and feet showed no abnormalities. The blood showed the following: hemoglobin 102 per cent (Sahli); red blood cells 6.35 to 7.28 million; hematocrit 0.62;

white blood cells 19,700; platelets 870,000 to 3.0 million. Because of the high platelet count and the consequent possibility of thrombosis, it was thought inadvisable to use phenylhydrazine, and the patient was therefore given a course of spray roentgen-ray therapy with resultant amelioration in symptoms and slight drop in red cell count. She failed to return for further observation.

*Case 15.* Mabel F., a Russian-Jewish housewife, was referred to one of us on March 13, 1937, the diagnosis of polycythemia already having been established at another hospital. In January 1937, she began to have numbness of the legs accompanied by pain in the back and pain radiating from the thighs to the ankles. Soon the legs, particularly the left one, became stiff, and she required assistance in getting into and out of bed. Finally, she developed constant "grinding" pain in both legs and found it difficult to walk about. She was told she had arthritis. In February 1937 she noticed a heavy sensation in the left upper abdomen and felt a large "lump." She was admitted to another hospital for study where the "lump" was discovered to be a very large spleen, and an erythrocyte count of 8.0 million was found. Few other symptoms were present except that she had noticed "sluggishness" for about a year and anorexia and "gas" for a few months. The past history was negative except that two years previously, following a dental extraction, she had bled for 18 hours, requiring packing of the tooth socket.

Examination on March 13 and at subsequent occasions when the patient was admitted to the hospital disclosed a plethoric-appearing woman, with slight cyanosis and marked flushing of the mucous membranes and conjunctivae. The retinal veins were greatly distended. The tongue was reddened. Examination of the chest, heart, and lungs was entirely negative. The liver edge was felt three to four fingers' breadth below the right costal margin; the spleen was extremely large, occupying the entire left upper quadrant. The blood pressure was 130 systolic and 90 diastolic. There was slight to moderate limitation in motion of the knee joints and the patient presented a somewhat spastic gait. The knee-jerks were hyperactive; the vibration sensation was normal. The disturbance in gait seemed out of all proportion to the physical findings. An orthopedist felt she had somewhat pronated feet and tight heel cords. Further observation pointed to a diagnosis of hysteria, at least as an associated phenomenon. The laboratory data were as follows: hemoglobin 123 per cent; red blood cells 8.63; white blood cells 10,800; polymorphonuclears 82 per cent (26 band forms), lymphocytes 6 per cent, monocytes 5 per cent, eosinophiles 5 per cent; basophiles 2 per cent. One nucleated red blood cell was seen. Platelets were 362,000; hematocrit 66 per cent. Basal metabolic rate  $+2$  per cent; gastric analysis—a maximum of 5 units of free HCl after an alcohol test meal; urines—albumin very slight trace on one of three occasions; sediment negative; non-protein nitrogen 39 and 31 mg.; uric acid 4.9 and 4.8 mg.

After the above studies were completed, the patient was venesected and placed on an iron deficiency diet. There was rapid subsidence of the symptoms referable to the legs, and within three months there was neither pain nor limitation in motion. The patient has remained well on an iron deficiency regimen without further treatment.

*F. Cases with "Nephritis" Outstanding.* Polycythemia may be confused with chronic vascular nephritis. A plethoric appearance may be common to both conditions. Furthermore, most cases of polycythemia in our series have shown hypertension, slight degrees of albuminuria, at times a few casts, and at times a definite although slight elevation in the blood non-protein nitrogen (table 3). In one of our cases, the diagnosis of severe nephritis seemed quite definite; when polycythemia was later discovered, the patient had an excellent therapeutic response following the institution of an iron-deficiency regimen.

*Case 16.* Rebecca G., a Russian-born Jewish housewife, aged 70 years, was admitted on June 17, 1936, in a state of mental confusion. She had been followed in the Out-Patient Department since August 1935. At that time she complained of severe headache of one year's duration, spells of weakness with a sensation of faintness in the past month, and a shooting pain in the left thigh a week previously, necessitating admission to the Emergency Ward. At this time albuminuria was discovered together with the presence of granular casts. The white blood cell count was 15,000. She had frequency of urination together with nocturia, 4 to 5 times. On examination the heart was found slightly enlarged, the blood pressure 200 systolic and 100 diastolic, the abdomen negative, and the urine showed a slight trace of albumin with a rare red blood cell and a rare hyaline cast. The blood non-protein nitrogen was 47 mg. per 100 c.c. The diagnoses of hypertension and chronic vascular nephritis were made and the patient placed on a low protein diet. In a few days, on account of recurrence of pain in the left leg, she was referred to the Orthopedic Clinic where no evidence of arthritis or sacroiliac disease was discovered. She was lost from ob-

TABLE III  
Laboratory Data

Case	Hgb. (Sahli) %	R.B.C. (Millions)	W.B.C.	Platelets (Millions)	Hematocrit %	Poly-morphs %	Blood Viscosity (Units)	Albu-minuria	N.P.N. (mg. %)	Blood Volume (Total c.c.)	B.M.R.	Gastric Analysis (Units of Free HCl)
1	120	7.61	14,100	.789	—	76	—	VST-ST	41	—	—	—
2	115	7.00	18,900	2.850	58	80	—	Neg.	42	10,100	+5 +0	—
3	116	7.60	14,000	1.350	—	84	—	Neg.	—	—	—	—
4	145	9.41	8,300	2.200	76	79	—	SPT-ST	42	6,370	+9 -6	40-50
5	170	11.00	12,300	—	76	80	—	LT	53	—	+38	—
6	124	8.96	12,400	1.240	68	84	—	T	32	—	+15 +11	—
7	150	8.70	12,000	.800	74-80	82	13.4	VST	—	6,700	-15	—
8	118	10.20	10,800	2.500	—	81	—	SPT	41	—	+5	—
9	130	9.95	—	.594	—	87	—	SPT-LT	44	—	—	—
10	124	7.36	21,300	1.140	—	81	—	VST-T	47	—	+50	—
11	124	7.24	9,800	1.500	—	78	—	Neg.	—	—	—	—
12	128	7.69	12,600	.898	64	93	—	Neg.	—	—	—	—
13	138	8.75	18,400	1.740	76	87	15-17	Neg.	—	8,900	+15	18
14	102	7.28	19,700	.870 to 3.000	62	75	—	Neg.	—	—	—	—
15	123	8.63	10,800	.362	66	82	10.0	O-VST	39	7,740	+2	5
16	140	9.70	15,400	.750	70	92	—	VST-T	56	—	—	—
17	150	8.27	13,500	1.200	67	84	—	ST-T	37-40	—	+13	—
18	104	9.00	18,000	1.000+	65	85	—	SPT-VST	30	—	+21	—
19	120	9.00	20,000	1.500	79	86	—	ST	35-41	12,000-15,000	+35	—
20	161	9.10	9,500	.660	82	78	14.0	VST	65	17,500	+23	—

servation until a second admission to the hospital on July 17, 1936. At that time, the following additional history was obtained: dimness of vision for about three years; hypertension and headaches for about two years associated with increasing weakness; an attack of extreme dyspnea occurring six weeks previously for which she had been admitted to another hospital and discharged in four days; extreme weakness for four weeks; headache, vertigo, tinnitus, impaired memory, and increasing mental confusion for about two weeks; vomiting on the day of entry.

Examination disclosed a red-faced, restless old woman who was obviously much confused. The skin and mucous membranes presented a dusky purplish coloration, and several small telangiectasiae were present on the face. There was bilateral arcus senilis and cataract formation. The conjunctivae were greatly injected. The tongue was thick, dry, and thickly coated. The heart was slightly enlarged to the left. The aortic second sound was somewhat accentuated. There was an occasional ventricular extrasystole. The peripheral arteries were thickened and tortuous. Blood pressure was 208 mm. of mercury systolic and 120 diastolic. The lungs showed a few râles at both bases. The liver edge was felt two fingers' breadth below the right



costal margin, and the spleen, which was thin and rather deep, was felt with some difficulty two fingers' breadth below the left costal margin. There was moderate clubbing of the fingers.

The urine showed a very slight trace to a trace of albumin; no casts were present at this time; specific gravity varied between 1.010 and 1.020. The blood examination showed the following: hemoglobin 140 per cent (Sahli); red blood cells 10.0 million; white blood cells 15,400. Further blood studies confirmed these findings: hemoglobin was between 130 and 145 per cent (Sahli); red blood cells between 8.7 and 9.7 million; platelets 750,000; reticulocytes 2.5 per cent; hematocrit 70 per cent. Frequent venesections were performed with striking benefit to the mental state and finally with complete relief of all the other symptoms.

*G. Cases with a Multiplicity of Symptoms Suggesting Neurasthenia.* The diagnosis of neurasthenia may either be made by exclusion or in a more positive fashion when a host of seemingly unrelated symptoms is present. In the case to be described the great multiplicity of symptoms suggested neurasthenia. The possibility is naturally present that both the "organic" disease polycythemia and the functional disorder "neurasthenia" were present together. However, the complete relief of all the symptoms when the blood was brought to a normal level, the return of identical symptoms with relapse to the polycythemic state, and again relief with appropriate therapy point to polycythemia as being the definite cause of the numerous symptoms.

*Case 17.* Flora S., a 55 year old Russian-Jewish housewife, first came to the Out-Patient Department in 1932. In 1924 she began to complain of frequency of urination, nocturia, vertigo, spots before the eyes, ease of fatigue, "pressing" feelings in the arms, thighs, chest, and rectum together with numbness and tingling of the fingers. A doctor told her she was suffering from "change of life" and high blood pressure (blood pressure 215). In June 1932 at the Out-Patient Department she presented a flushed face, a large "geographic" tongue, a slightly hypertrophied heart with a soft systolic murmur, and a blood pressure of 182/108. Several urine specimens showed the presence of traces of albumin and occasional hyaline and granular casts. The diagnoses of hypertension, early hypertensive heart disease, and neurasthenia were made; nephritis was considered because of the urinary findings.

From June 1932 to October 1933, the patient was treated symptomatically in the Out-Patient Department, especial emphasis being laid on the neurasthenic state and hypertension. In October 1933 a physician suspected the possibility of polycythemia on account of the patient's plethoric appearance. The blood showed hemoglobin (Tallqvist) 85 per cent; red blood cells 7.89 million; white blood cells 23,000. The diagnosis of polycythemia was then made. Further studies demonstrated a warm, moist skin, congested conjunctival blood vessels, greatly reddened mucous membranes, large red tongue, cardiac enlargement, hepato- and splenomegaly, and large red hands and feet. The laboratory findings were: hemoglobin 150 per cent (Sahli); red blood cells 8.27 million; white blood cells 13,500; hematocrit 0.67; bilirubin 0.97 mg./100 c.c.; basal metabolic rate + 13 per cent. With control of the patient's hemoglobin and red cell counts first by phenylhydrazine, and more recently by an iron-deficiency regimen, the patient has lost all of her numerous symptoms and feels entirely well.

*H. Cases with Symptoms Referable to Several Systems or Difficult to Classify.* As already brought out, most cases of polycythemia present a multiplicity of symptoms, although emphasis is usually placed upon one or

another bodily system. In a few cases the complaints are referable to most of the systems without any single one being especially selected.

*Case 18.* Myer A., a 60 year old Russian-Jewish cantor, first entered the hospital on June 29, 1929. In 1924 he had been studied at another hospital where the diagnosis of polycythemia had been made and the following history obtained: easy fatigue for three years, increasing weakness for eight months, increasing dyspnea for about two months, gastric distress, and severe pains in the legs. Examination at that time showed bluish-red cyanosis of the face, injected conjunctivae, engorged fundal veins, deeply red mucous membranes, cardiac enlargement with a systolic murmur, splenomegaly (three fingers' breadth), and clubbed fingers. The blood pressure was 150 systolic, 80 diastolic. Hemoglobin was 170 per cent; red blood cells 10.7 million; white blood cells 10,500; platelets 350,000. Basal metabolic rate was +33 per cent. The urine showed a slight trace of albumin. After two venesections and one short course of benzol therapy, the patient was discharged from the hospital. In 1926 he was troubled chiefly with severe upper abdominal pain and on one occasion went into collapse. He was later found to have a gastric ulcer which had perforated into the lesser omental sac. In 1927 and 1928 he was troubled chiefly with dyspnea, weakness, and pains in the legs. Auricular fibrillation developed, and he was thought to have coronary thrombosis. The blood pressure was 150 systolic and 90 diastolic. The hemoglobin was between 150 and 165 per cent; red blood cells between 6 and 10 million. Courses of phenylhydrazine and roentgen-ray therapy were given without definite relief.

At the Beth Israel Hospital in 1929, he complained of headache, poor vision, increasing deafness, extreme weakness, marked dyspnea, anorexia, constant right upper quadrant pain, and severe pains in the legs chiefly at night. Examination showed a very red, roughened tongue, irregular reddened spots on the soft palate, auricular fibrillation, and a large liver and spleen. The hemoglobin was 104 per cent (Sahli); red blood cells 9.0 million; white blood cells 18,000; polymorphonuclear cells 85 per cent; blood platelets more than a million per cu. mm.; hematocrit 65 per cent. The urine showed a very slight trace of albumin. A sternal bone-marrow biopsy showed extreme hyperplasia, particularly of the erythro-normoblastic series. While in the ward, he complained chiefly of cramplike pains in the legs mostly nocturnal, unrelieved by heat and rest, and relieved somewhat by walking. In 1930 the pains in the legs dominated the clinical picture. The dorsalis pedis and posterior tibial arteries were readily felt, although they showed evidence of much sclerosis. Treatment for the polycythemia with occasional venesections, phenylhydrazine, etc. was uniformly unsatisfactory.

In 1931, 1932, and 1933, frank congestive failure was present. By 1934 the liver and spleen had become greatly enlarged, occupying almost the entire abdomen. At this time he showed definite anemia: the red cell count was 3.15 million, hemoglobin 80 per cent (Sahli). The leukocyte count was normal, the platelets 1.50 million. The stained smear showed 10 per cent myelocytes, and there was marked variation in size and shape of the red cells. Shortly thereafter the patient died.

*Case 19.* Hyman A., a Russian-Jewish tailor, aged 45, first came to the Out-Patient Department in 1929 complaining of a lesion of the upper lip of four years' duration. The diagnosis of sycosis ("barber's itch") was made and many methods of therapy were tried without relief. In May 1932 the patient appeared in the Medical Clinic complaining of severe frontal headache of two months' duration, epigastric distress, and constipation. On examination it was noted that the face was flushed and slightly cyanotic and that the mucous membranes and conjunctivae were injected. The radial arteries appeared to be unusually hard and tortuous. The blood pressure was 148 systolic and 100 diastolic. The clinical diagnoses of chronic constipation and premature arteriosclerosis were made. The patient continued to complain, and

chiefly because of the red color of the face a blood examination was made which showed the following: hemoglobin 100 per cent (Tallqvist); red blood cells 7.97 million; white blood cells 14,700; polymorphonuclear cells 85.5 per cent; platelets 815,000. The diagnosis of polycythemia vera was made at this time. Several teeth were extracted with the resultant loss of a great deal of blood. The patient was not seen for one year thereafter. In the Dental Clinic in 1933 he was found to show striking congestion of the mucous membranes without any apparent inflammation, and again the diagnosis of polycythemia was made. At that time, the hemoglobin was 108 per cent (Sahli) and red blood cells 9.18 million. The basal metabolic rate was +23 per cent. Again the patient was lost from observation until 1935 when he was found in the Skin Clinic receiving injections of manganese for the still present syeosis. Severe pain had developed in the left buttock at the site of several of the injections. The pain became so severe as to necessitate admission to the House.

At this time (September 2, 1935), the history was obtained of headache for 10 years, vertigo 4 years, and a multiplicity of symptoms for 2 years. These were lassitude, insomnia, weakness, fullness in the head, loss of memory, dimness of vision, tinnitus, occasional attacks of epistaxis, dyspnea, and palpitation on exertion, occasional substernal oppression, easy fatigability, a sense of fullness in the stomach, frequent nausea with occasional spells of vomiting, epigastric pain, pain in the left upper quadrant, and severe constipation. In August 1934 transient right-sided paralysis of the face, right arm, and right leg had occurred. Also present were numbness and tingling of the extremities and increasing deafness.

Examination on September 2, 1935, showed a little man with extreme ruddy cyanosis (he appeared to be in a constant blush), especially noticeable over the cheeks, the tip of the nose, and the ears. The mucous membranes were deeply cyanosed. Over the left upper lip there was a raised, purple area measuring 2 by 0.5 cm. Ophthalmoscopic examination showed a deeply colored retina with striking engorgement of the retinal veins and marked tortuosity of the vessels. The tongue was very large, beefy red, and thickly coated. Engorged superficial veins were present over the scalp and neck. No abnormalities of the heart or lungs were noted. There was marked dilatation of the superficial abdominal veins. The edge of the liver was felt two fingers' breadth below the right costal margin, and the spleen was felt in a similar position on the left. The finger tips were greatly cyanosed and there was slight thickening of the terminal phalanges. The toes showed striking cyanosis and the nails were greatly thickened. The peripheral arteries of the feet and legs were readily palpable. Over the left buttock there was a swelling the size of a small orange, very tender to touch.

The laboratory findings were now as follows: hemoglobin between 110 and 130 per cent; red blood cells 8 to 10 million; white blood cells 13,000 to 30,000; hematocrit 0.77 to 0.79; platelets 1,630,000 to 2,050,000 with a platelet volume of 1.5 per cent. The total blood volume was 12,000 to 15,000 c.c. The capillaries of the nail bed showed marked dilatation, and great tortuosity with many "figures of eight." The urine showed a slight trace of albumin. The basal metabolic rate was +35 per cent, bilirubin 1.92 mg./100 c.c. Needle aspiration of the swollen buttock showed old blood. At operation a large hematoma was discovered, the source of blood being an artery of moderate size which was partially covered by friable thrombus. This was ligated. Subsequently, the patient was venesected a number of times and placed on an iron-deficient diet with complete relief of symptoms. In 1936, however, he complained of distress and nausea occurring one-half to one hour after meals. Roentgen-rays of the gastrointestinal tract revealed slight irregularity of the lesser curvature aspect of the duodenum suggesting either ulcer or periduodenal adhesions. The symptoms were quickly relieved by a bland diet.

*Case 20.* Samuel C., a 62 year old Russian-born Jewish shoemaker, was referred to one of us in May 1937 for diagnosis of possible polycythemia. Six years

previously prostatectomy had been performed for hypertrophied prostate. Two years before he had noticed an increasing redness of the face and head and particularly of the nose; during the summer, his skin felt unusually warm and its redness always excited comment. For about a year he had felt a throbbing sensation in the head almost constantly and two months ago had noticed reddish nodules of the eyelids with a troublesome burning sensation. He was referred to a dermatologist for a possible skin condition, and the diagnosis of polycythemia was indicated. Examination revealed a small man with extreme reddish cyanosis of the lips and mucous membranes and an almost startling redness of the face and particularly of the nose. Many small nevi were present. The conjunctivae showed striking congestion with the presence of two pea-sized subconjunctival nodules, one in each eye. The retinal veins were greatly distended, the arteries being narrowed and tortuous with "silver-wire" effects. The tongue was large with a normal coat. The chest showed some increase in antero-posterior diameter. The heart was not enlarged and showed no abnormal findings. The blood pressure was 165 systolic and 110 diastolic. The liver was not felt, but the edge of the spleen was felt one finger's breadth below the left costal margin. There was marked sclerosis of the peripheral arteries. The laboratory data were as follows: hemoglobin 161 per cent; red blood cells 9.10 million; white blood cells 9,500; platelets 660,000; hematocrit 81 to 82 per cent; total blood volume 17,500 c.c. with plasma volume 3320 c.c.; urine, very slight trace albumin in all specimens, sediments negative; non-protein nitrogen 65 mg.; creatinine 2.2 mg.; basal metabolic rate  $+23$  per cent.

The patient required a large series of venesections and was then placed on an iron-deficiency diet. There was remarkable subsidence in the redness of the skin and in the conjunctival congestion, although the nodules were still present. When the hemoglobin and erythrocyte count had reached normal levels, the blood pressure became diminished to 126 systolic and 70 diastolic, the urine failed to show albumin, and the blood non-protein nitrogen was reduced to 40 mg./100 c.c. The chronic conjunctivitis finally subsided entirely.

### ANALYSIS OF CASES

*Symptoms.* An analysis of the symptoms encountered in this series of cases is presented in table 3. Neuropsychiatric symptoms predominated. Headache, usually quite severe, was present in 17 of the 20 cases; in 3 cases, typical attacks of migraine had been present for years. Vertigo was complained of in 14 cases. Various types of visual disturbances, particularly spots before the eyes, were frequently encountered, and in 6 cases colored scotomata were present. Paresthesias of the extremities—numbness and tingling—were present in 12 cases. Weakness, so common to many conditions, was complained of in 8 cases. Next in frequency to the neurological symptoms were those referable to the abdomen or the gastrointestinal tract. Thus abdominal pain was complained of in 10 cases; constipation was present in all but 6 cases. In 4 cases a peptic ulcer was found and in a fifth case suspected. Cardiovascular symptoms were common: thus dyspnea, palpitation, precordial pain, etc. were present in 8 cases; circulatory disturbances of the legs, feet, or hands were present in 6 cases; and various types of thromboses (cerebral, coronary, venous, arterial) were present in 9 cases. The symptoms referable to the extremities were among the most interesting. Several patients stated that their hands had always been red, warm, and moist, and tended to become swollen in hot weather. Two patients had the

typical symptoms of thromboangiitis obliterans, and in another case the diagnosis of erythromelalgia was made. In 3 other patients symptoms suggesting erythromelalgia, i.e. pain in the legs, aggravated by heat and dependency and improved by cold were present, and at times became a prominent complaint.

An interesting feature was the marked tendency to bleed, especially following operative procedures, however simple. Thus in Case 1 there was marked bleeding from a gastric ulcer; in Cases 3, 10, 11, 12, 17 and 19 severe bleeding from the gums occurred after dental extraction, necessitating packing and suturing in several instances. In Case 19, severe bleeding with the formation of a hematoma in the gluteal muscles occurred after an intramuscular injection; in Case 11, large hematomas in the incisional wound formed after appendectomy, and there was a great deal of oozing at the time of operation.

The most constant feature of the symptomatology was, however, the multiplicity of symptoms. Thus, it was quite unusual to find the patient complaining of only two or three symptoms; in most cases, symptoms referable to every part of the body were described.

*Salient Physical Signs.* A plethoric appearance of the face, with dusky, purplish-red lips, congested conjunctival blood vessels and red ears was present in every instance and was usually responsible for the diagnosis being suspected. The color, to use Osler's phrase, was as "red as a rose" in the summer, but tended to become much duskier and more cyanotic in the winter. The hands participated in the general plethoric appearance and were often beefy red in appearance; in the winter when the patient first appeared from outdoors, they were usually blotchy and blue, gradually becoming unnaturally pink on exposure to the warm air. The feet also showed the same phenomena.

Another constant sign was the presence of greatly distended retinal veins, their deep blue coloration contrasting sharply with the red of the arteries. Congested buccal mucous membranes were common to all cases. The tongue was usually large and thickly coated; in 10 cases, it was in addition deeply fissured, i.e. geographic.

A palpable liver was present in 15 instances; usually it was felt about two fingers' breadth below the right costal margin but at times, as in Cases 11 and 12, it was unusually large, extending to the umbilicus, and quite tender. In both of these cases the chief complaint was of pain in the right side of the abdomen, diagnosed in one case as appendicitis, in the other as gall bladder disease. A palpable spleen was present in 16 cases. It was firm and elastic in the early cases, extending from one to four fingers' breadth below the left costal margin; in the long-standing cases, it became extremely hard and occasionally extended to the pelvic brim. In four cases the spleen could not be felt.

The blood pressure reading was of great interest because of the statement so commonly made that the blood pressure in polycythemia is normal.<sup>14</sup>

In 11 cases, it was above 140 mm. Hg systolic, and in 7 instances was 170 mm. Hg or over. Readings of 200 mm. or over were found in three cases. Thus hypertension was present in the majority of the cases. Gaisböck,<sup>15</sup> some years ago, discriminated a special group of cases of polycythemia, distinguished by hypertension and lack of splenomegaly. He stated that true polycythemia was always associated with a normal blood pressure. It may be noted from table 2 that all of our cases with hypertension also showed splenomegaly.

Other abnormal physical signs were present in many cases: various types of cardiac lesions, certain neurological findings, such dermatological manifestations as hemangiomas, and vascular nevi. The outstanding features were, however, associated with the "plethora vera" of the ancient writers: red face, hands, and feet; congested lips, buccal mucous membranes, conjunctivae; dilated retinal veins; enlarged spleen and liver. As noted below, these were in all probability the results of a chronically overdistended vascular system due to an increased blood volume.

*Laboratory Data.* Certain of the laboratory data are recorded in table 3. These will not be extensively commented upon here, but it may be noted that (1) the hemoglobin percentage varied from 104 to 170 per cent of normal, (2) the red cell count from 6.70 to 11.0 million per cu. mm., (3) the white cell count from 8,700 to 21,300 per cu. mm., (4) the platelets from 594,000 to 2,850,000 per cu. mm., (5) the polymorphonuclear cells from 74 to 93 per cent, (6) the total blood volume from 5,450 c.c. (after hemorrhage) to 17,500 c.c., (7) the basal metabolic rate from — 19 per cent to + 50 per cent. The urine usually showed albumin and at times casts (cf. Gram<sup>16</sup>), and the blood non-protein nitrogen was at times elevated above 40 mg. per 100 c.c. Thus, despite the rather marked variability in findings, the following was true of the great majority of the cases: an increase in the hemoglobin, the red cell count, the leukocyte count, the polymorphonuclear percentage, the platelet count, and blood volume. Microscopic examination of the capillaries at the nail bed showed uniformly an increased tortuosity and distention of the capillary loops, most pronounced in the venous limbs.

Sternal bone marrow biopsy was performed in eight cases. In every instance the marrow showed a generalized hyperplasia involving *all* of the cellular elements: normoblasts, myelocytes, and megakaryocytes (i.e. "pan-myelosis"). In some instances, the increase in megakaryocytes was very striking, as many as 6 to 10 megakaryocytes being seen per high-power field.

### THE DIAGNOSIS OF POLYCYTHEMIA

Enough has already been stated to indicate that patients with polycythemia may be overlooked for years, and it is likely that many cases are never correctly diagnosed but masquerade under the diagnoses of neurasthenia, various types of peripheral vascular disease, hypertension, heart disease, and nephritis. As in many other rather uncommon diseases, the diagnosis may be overlooked unless it is considered; it is possible, however,

to obtain definite suggestions from the history or the physical examination which may lead one to suspect the diagnosis.

The racial origin of the patient is important. All our cases were Jewish. The high incidence of polycythemia among Eastern European Jews was first pointed out by Reznikoff, Foot, and Bethea.<sup>5</sup> In a series of 134 patients, 47.8 per cent were Jews of Eastern European origin whereas the same racial element accounted for only about 9 per cent of the same general hospital population. In our own series, only two were other than Russian or Polish Jews. The material is of course drawn from a Jewish hospital and a predominantly Jewish clientele; but the contrast between the racial types in our cases of polycythemia and pernicious anemia is striking. Discussion with physicians in charge of the blood clinics at other hospitals of Boston has shown that the cases of polycythemia are ordinarily found among Jewish patients. It should be noted, however, that in the group of cases of polycythemia studied by Blake (Thesis)<sup>17</sup> at the Peter Bent Brigham Hospital (1913 to 1936) the proportion of Jewish patients was only about 14 per cent, which was about the proportion of Jewish patients in the general hospital population.

Other suspicious points in the history are: (1) multiplicity of symptoms, especially relating to the central nervous system, (2) complaint of severe headaches, including migraine, (3) complaints referable to vascular disease of the extremities, (4) history of multiple thromboses, venous and arterial, especially of the extremities, (5) history of severe bleeding following even slight operative procedures. These symptoms although not pathognomonic may lead one to suspect the possibility of polycythemia.

In the physical examination, one looks particularly for high facial coloring, the appearance of reddish cyanosis, highly colored mucous membranes and conjunctivae, dilated retinal veins, a thickly coated and fissured tongue, a large spleen and liver, thick red hands and feet, and hypertension. Examination of the spleen is particularly important and should be carefully made. Percussion of splenic dullness, if performed routinely, is frequently of service in detecting slight enlargement of the organ which cannot be felt unless it is about twice its normal size. Palpation, unless systematically done, may result in failure to feel the spleen entirely. The location of the spleen varies considerably; it may be felt far out towards the flank or near the epigastrium; at times, instead of occupying its usual anterior position, it is situated rather deeply; at times, paradoxically enough, it is so large that the observer in placing his hand just under the costal margin does not feel the lower pole which may be below the umbilicus.

The final diagnosis is made by performance of certain laboratory tests. It is of no value whatever to do a Tallqvist hemoglobin determination in suspected cases, since above the reading of 80 per cent the Tallqvist scale is worthless. The hemoglobin test should therefore be done either by the Sahli or some other relatively accurate method. The erythrocyte count is the central point of the diagnosis and will, with rare exceptions, as discussed

below, immediately confirm or disprove the clinical impression. Before further consideration of polycythemia is entertained, the count should at least be 6.0 millions per cu. mm. The leukocyte, differential, and platelet counts are important in indicating general bone marrow activity. Particularly is this true of the platelet count, which we have come to rely upon as of great importance in diagnosis. Platelet polycythemia ("thrombophilia") has in certain cases been the outstanding feature. Other tests of value are the hematocrit determination, which should be done in every suspected instance, and the blood volume. Estimation of the blood volume<sup>18</sup> has occasionally proved of confirmatory importance in diagnosis of the doubtful case. The normal total blood volume is about 85 c.c. per kg. of body weight or about 5000 to 6000 c.c. It varies directly with the height and weight but especially with the surface area. The plasma volume is normally about 2700 c.c. and about 50 c.c. per kg. In polycythemia vera, as Rowntree and Brown<sup>18</sup> have pointed out, one of the constant features is the striking elevation not only in the total blood volume but in the cell volume ("polycythemic hypervolemia"). It is due to this great increase in blood volume—the general plethora—that the majority of the symptoms and signs are undoubtedly present.

Examination of the capillaries at the nail bed may occasionally be of importance. In polycythemia vera, as pointed out by Brown and Giffin,<sup>19</sup> the capillaries have a characteristically altered appearance: they are very large, tortuous, dilated, and exhibit great distention of the venous limbs. It should be noted that these changes correspond closely to the condition of the retinal blood vessels which show marked dilatation of the veins. It is not known whether these changes are secondary to the increased blood volume or "primary" and thus part of a circulatory abnormality which may be the etiological factor in the disease.

The sternal bone marrow biopsy may occasionally be of diagnostic value and is always of great interest from the pathological standpoint. In every case of polycythemia the marrow is intensely hyperplastic, all the cellular elements—red, white, and megakaryocytic—participating. Of diagnostic importance in certain cases is the extremely large number of megakaryocytes which crowd the sections. Reznikoff et al.<sup>5</sup> have pointed out that the capillaries and arterioles of the marrow show much thickening of the intima and media, which they believe leads to an increased degree of anoxemia of the marrow and thus to polycythemia.

In summary, there are certain symptoms, signs, and laboratory tests which when pieced together spell the diagnosis of "primary" or "true" polycythemia. We have come to rely upon the following group of data as being of diagnostic value:

*Symptoms:* Headache, vertigo, visual disturbances, colored scotomata, paresthesias  
Symptoms referable to vascular disturbances of the extremities  
History of profuse hemorrhages after minor trauma  
History of venous and arterial thrombosis  
Multiplicity of symptoms



- Signs:* Plethoric appearance of the face and conjunctivae  
 Dilated retinal veins  
 Thickly coated and fissured tongue  
 Splenomegaly, hepatomegaly  
 Red hands and feet
- Laboratory:* Elevated erythrocyte count (above 6.0 million per cu. mm.)  
 Elevated hemoglobin percentage  
 Elevated leukocyte count  
 Elevated polymorphonuclear percentage  
 Elevated platelet count  
 Elevated hematocrit  
 Elevated blood volume  
 Distended capillaries  
 Sternal bone marrow biopsy: Red cell hyperplasia, megakaryocytic hyperplasia  
 Elevated basal metabolic rate (cf. Bliss<sup>20</sup>)

It should be emphasized that not *every* symptom, sign, or available bit of laboratory evidence is present in every example of the disease. We believe that the following minimal data should be present before a definite diagnosis of primary polycythemia is made: plethoric appearance, spleno- or hepatomegaly, definitely elevated erythrocyte count, elevated platelet count, elevated hematocrit. In a doubtful case, the procedures of blood volume estimation and capillary microscopy may be helpful.

### DIFFERENTIAL DIAGNOSIS

1. *The Doubtful Case.* Chiefly because of our increasing interest in the diagnosis of primary polycythemia we have been led to examine many cases which present certain features suggestive of the disease. The decision for or against the diagnosis has at times been an extremely difficult one and has frequently required a long period of observation during which opinion might often be changed. Among these doubtful cases were the following:

*Albert T.*, a 27 year old Italian attorney, complained of vague aches and pains. For some years his hands had been blotchy, warm, and perspiring, and blotchy red spots frequently appeared on both the hands and feet. Examination showed a healthy appearing young man with warm, moist, blotchy hands and feet. There was no definite plethora, the retinal veins were not distended; and the spleen and liver were not felt. Routine blood studies showed: hemoglobin 96 per cent; red blood cells 6.49 million; white blood cells 7500; polymorphonuclears 57 per cent. Because of the slight elevation in erythrocyte count, several counts were made; these varied from 6.20 to 6.96 million per cu. mm. Other laboratory studies showed: hematocrit 0.55; platelet count 496,000; total blood volume 7500 c.c.; capillary microscopy disclosed marked tortuosity and irregularity in the diameter of the capillaries of some nail beds and narrowing of the capillaries in others. These findings were thought to be consistent with vasomotor instability. It was decided that the diagnosis of polycythemia was not at present justified despite the elevation in erythrocyte count and the slightly increased plasma and total blood volume because (1) the leukocyte count was normal, (2) the polymorphonuclear count was normal, (3) the platelet count was normal, (4) the spleen was not palpable. No explanation for the erythrocytosis was made except possibly on the basis of vasomotor changes of the extremities. Whether the

diagnosis of polycythemia vera will become more evident in future years remains to be seen.

*David S.*, a 60 year old Russian-Jewish tailor, complained of burning pains in the feet aggravated by exercise, relieved slowly by rest. Examination in 1934 disclosed a slightly plethoric appearance, spider telangiectases of the face, moderate emphysema of the lungs, slight cardiac enlargement, blood pressure 170 systolic and 100 diastolic, irregular blotches of the feet, readily palpable dorsalis pedis arteries. The blood findings were: hemoglobin 92 per cent; red blood cells 5.23; white blood cells 10,000 to 13,500 with 67 per cent polymorphonuclears. The patient improved with rest in bed. In 1935 he was referred to the Blood Clinic because of possible polycythemia. At this time, examination showed a somewhat plethoric man with slight cyanosis of the lips. The retinal veins were not distended, and the spleen and liver were not felt. The blood findings were: hemoglobin 98 per cent; red blood cells 5.53; platelet count 1,680,000 to 1,960,000; hematocrit 0.52; blood volume 4900 and 5200 c.c. It was felt that the findings were at present inadequate to justify the diagnosis of polycythemia vera: the red cell count showed no definite elevation, the spleen was not palpable, and the blood volume was not elevated. The circulatory changes in the extremities in association with readily palpable arteries and very high platelet count suggested, however, the possibility of multiple small thromboses on the basis of a very high platelet count (cf. Nathan W., Case 15). Further follow-up studies are essential in determining this possibility.

*Philip Z.*, a 27 year old Jewish glazier awaiting herniorrhaphy, was referred to the Blood Clinic from the Surgical Service because of suspected polycythemia. In addition to a very plethoric appearance, a red cell count of 6.16 million had been found. The patient said he had "always" had a red face and hands, which became blue with cold and very red with warmth. Otherwise, he had no symptoms except those referable to the hernia. Examination disclosed an extremely red-faced individual with a slight tinge of cyanosis. The conjunctival blood vessels were markedly congested and the retinal veins slightly distended. The spleen and liver were not felt. The hands and feet were deeply red and somewhat cyanotic. The blood findings were as follows: hemoglobin 100 per cent (Sahli); red blood cells, 6.08, 6.16, and 6.70 million at successive examinations; white blood cells 5700; polymorphonuclears 68 per cent; platelets 630,000; hematocrit 0.51; blood volume 6200 c.c. Because none of the findings except the erythrocyte count were at all suggestive of polycythemia vera, the operation of herniorrhaphy was performed; no unusual bleeding took place. This case must be classified as an example of erythrocytosis, possibly normal, possibly associated with some disturbance of the vasomotor system (cyanotic appearance of the face and hands). Whether this case is a very early example of polycythemia remains to be seen.

*Dr. S.*, an Irish-American physician, aged 52, was referred by a neurologist for study of a possible hematological abnormality. In October 1934 and February 1935 he had typical epileptic convulsions. A physician in October 1934 found, in the course of routine laboratory work, that the hemoglobin (Tallqvist) was 70 per cent and the red count 6.50 million. Another physician, in evaluating these data, advised the patient to take iron because of "secondary anemia." Several hemoglobin estimations by the Tallqvist method gave readings in the vicinity of 70 per cent. An intern at the physician's local hospital told the patient he had "hypochromic anemia" and advised even more iron. A neurologist failed to find evidence of anemia and made the diagnosis of idiopathic epilepsy. The patient stated he had had a "high color" for many years and for 13 years had had "indigestion" with a sense of fullness in the right upper quadrant and much belching.

Examination disclosed a large plethoric appearing man. There was definite reddish cyanosis of the lips and buccal mucous membranes. The conjunctivae were reddened and there was dilatation of the fundal veins. The edge of the liver was felt

three fingers' breadth below the right costal margin; the spleen could not be felt. The hands were large, blotchy, and the finger tips were bluish. The blood pressure was 144 to 160 systolic and 90 diastolic. Neurological examination was negative.

The urine showed no albumin, sugar, or casts. The blood showed: hemoglobin 107 per cent (Sahli); red blood cells 6.70 million; white blood cells 7500; differential count: polymorphonuclear cells 74 per cent, lymphocytes 19 per cent, monocytes 7 per cent; platelet count 680,000.

He was given phenylhydrazine hydrochloride at first 0.150 gm. daily, then 0.030 gm. daily, and later 0.030 gm. two to three times weekly. This effectively controlled the hemoglobin and erythrocyte counts. About a month after the erythrocyte count had reached a normal level, the patient's digestive symptoms had completely gone and the liver edge could not be felt. The epileptic attacks continued although they gradually became much diminished in severity and lessened in frequency. For 11 months he had complete freedom from attacks, which then recurred, even though the hemoglobin and erythrocyte counts were at normal levels.

Although this patient was first considered a definite but mild example of polycythemia, he was later placed in the doubtful group because (1) the convulsive symptoms recurred even though the erythrocyte count was retained at a normal level, (2) the leukocyte and platelet counts were normal, (3) the spleen was never palpable, and (4) the blood volume was normal.

2. *Polycythemia Secondary to Known Cause.* These cases should not ordinarily offer any diagnostic difficulty. The finding of polycythemia in the presence of a chronic pulmonary lesion such as bronchitis, bronchiectasis, asthma, or of a chronic right-sided cardiac lesion whether acquired or congenital should almost automatically result in the diagnosis of secondary polycythemia. We have studied several patients of this type, some of them typical examples of "Ayerza's disease": cyanosis, polycythemia, chronic right-sided heart failure, pulmonary hypertension, ? pulmonary arteriosclerosis. The blood always shows evidence of arterial unsaturation, a finding never present in true polycythemia. Although the hemoglobin, erythrocyte count, hematocrit, and even blood volume may be as greatly elevated as in polycythemia vera, there is usually no elevation of the leukocyte, polymorphonuclear, or platelet counts.

#### COMMENT

The diagnosis of a condition seen only rarely in everyday practice usually rests first upon thinking of the possibility of its presence and second upon attempting to prove or disprove this by appropriate tests. We gradually become familiar with our errors in diagnosis which may often be directly traced to failure to think of a given possibility. Too often we are accustomed to make the obvious diagnosis and to disregard the possibility that "hypertension," "menopause," or "migraine" might in reality not be the ultimate diagnosis but rather symptomatic expressions of some more general and more serious organic disorder. The first element in the diagnosis of a rare disease is in the suspicion that it might be present. In the case of polycythemia, this suspicion is frequently obtained at the first interview with the patient. A plethoric individual should always be suspected. Multi-

plicity of symptoms, persistent headaches, vascular disorders of the extremities should make one at least wonder about the possibility of polycythemia.

Once suspicion has been aroused, careful search should be made in the history, the physical examination, and the laboratory data for proof of presence or absence of the condition. Whatever the cause of the disease may be, it is certain that the continuous overproduction of red blood cells results in great overdilatation of the entire circulation and stasis of blood in the vessels with the production of the many symptoms and signs which have been listed. The physical examination should lean heavily upon search for the evidences of an engorged circulation. The laboratory data will be the determining factors. No reliance whatever can be placed on a Tallqvist hemoglobin test alone; a red cell count at least must be done. If this is only slightly elevated, it should be repeated until a level is obtained. In doubtful cases particularly, the remainder of the laboratory data is of utmost importance, the leukocyte and polymorphonuclear counts and particularly the platelet count being determining factors. Examination of the capillaries at the nail bed and estimation of the blood volume may be differential features in certain cases. No one test, except possibly a constantly and greatly elevated erythrocyte count is of pathognomonic diagnostic significance. In doubtful cases, all the factors pointing to polycythemia should be balanced with those pointing against the diagnosis; it should be appreciated that certain of these factors may be lacking. To summarize: the diagnosis of polycythemia, at first suspected by the patient's appearance and symptomatology, is confirmed by the physical examination, and finally made or disproved through certain simple laboratory procedures.

#### SUMMARY AND CONCLUSIONS

1. Polycythemia vera is probably more common, particularly among Jews, than is ordinarily suspected. Its apparent rarity may, in some measure at least, be due to frequent lack of recognition.

2. The disease may masquerade for months to years under many different guises; among others may be listed neurasthenia, migraine, cardiovascular and renal disease, gastrointestinal disorders, and peripheral vascular disease.

3. The diagnosis of polycythemia vera in a plethoric individual may be suspected from certain points in the history: multiplicity of symptoms, vascular disturbances of the extremities, symptoms referable to the nervous system. Physical examination may confirm the first impression of possible polycythemia by the finding of dilated retinal veins, splenomegaly, a thickly coated fissured tongue, and red hands. The final diagnosis is usually made by the laboratory data.

4. The laboratory data in typical cases show not only an elevated erythrocyte count but an increase in all the elements formed in the bone marrow, i.e. leukocytosis, increase in polymorphonuclear cells, and a high blood

platelet count. The hematocrit and blood volume show increased values. Albuminuria is commonly found, and occasionally casts are present. The blood non-protein nitrogen is frequently slightly elevated.

5. Certain borderline, doubtful, or early cases of polycythemia are difficult of exact diagnosis. In these, recourse must be made to repeated studies over a long period of time. The final diagnosis is made by careful consideration of all the various factors in the history, the physical status, and the laboratory examinations.

6. The greatly overdistended circulation of polycythemia results in symptoms referable to many bodily organs. For this reason, polycythemia vera should be considered in the differential diagnosis of such unrelated conditions as neurasthenia, brain tumor, migraine, chronic nephritis, vascular hypertension, chronic cardiovascular disease, peptic ulcer, peripheral vascular disease, and even hemorrhagic diathesis. When the Tallqvist hemoglobin scale is discarded and use of the red blood cell count increased, the number of diagnostic errors should diminish.

#### APPENDIX

##### *The use of an iron deficiency regimen in the treatment of polycythemia.*

We first utilized this method following our experience with Case 1.<sup>8</sup> The sustained diminution in hemoglobin which followed several severe hemoemses and the use of the Sippy diet was thought to be due to the development of an iron deficiency state. In a series of 10 successive cases of polycythemia, previously poorly controlled by phenylhydrazine, acetylphenylhydrazine, roentgen-ray therapy, and other measures, there was complete clinical and symptomatic relief for 6 to 24 months following the induction of an iron deficiency regimen. This is accomplished by systematic venesections. The use of a diet poor in iron is probably of value in maintaining the iron deficiency state. An average case with hemoglobin of about 150 per cent, erythrocyte count of about 9-10,000,00 per cu. mm., and hematocrit of 65 to 70 per cent requires two venesections weekly for three to four weeks, rarely longer. The hemoglobin is reduced to less than 85 per cent, the hematocrit to less than 48 per cent, and the red cell count to less than 5.5 million. The hemoglobin and hematocrit readings are the important factors in the follow-up of the case, the erythrocyte count being of secondary importance. The red cells become hypochromic and microcytic, i.e. a hypochromic, microcytic "anemia" develops. The marrow continues to produce large numbers of cells, and the erythrocyte count may increase gradually to levels of 6 to 7 million or over, but for several months without further therapy the total circulating mass of red blood cells<sup>9</sup> (which depends upon the hematocrit and blood volume) remains low. When finally, the hemoglobin and hematocrit return to high levels and symptoms recur, only a few venesections are necessary to restore the state of iron deficiency. The diet given contains no meat or eggs and has an iron content of approximately 6 mg. per diem.

Patients on a normal iron intake (12 to 25 mg. of iron daily) usually require venesections at shorter intervals than those on a deficient iron intake.

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## SOME ASPECTS OF THE PSYCHONEUROSES\*

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FOR practical purposes the psychoneuroses may be viewed as "exhibitions of maladjustment" of the individual to his environment. The term maladjustment has been subject to considerable criticism and discussion. Some have interpreted it as applying only to the reactions of the individual to situational factors, others have used it as a yardstick in the differentiation of the psychoses and the psychoneuroses, while to many the term is merely an unsatisfactory ambiguity.

In its broadest sense it would appear that maladjustments may involve *physiological* as well as *psychological* considerations—reactions of the total organism to environmental changes interpreted as hostile or threatening to the safety of the whole. Environment may be exogenous or endogenous. In the former case, it is composed of situational factors which confront all human beings, sex, home, health, race, money, career, religion and social life; factors which swing from assets (when satisfactory adjustments are made) to liabilities (when maladjustments occur). These situations are exogenous in the sense that while they profoundly affect the individual they also involve other people, impose abstract ideas and bring into play the inter-reactions of a person to a group.

Endogenous environment comprises a vast physiological pattern, the physique of the individual, his endocrine reactions, autonomic nervous system, biochemistry, and somatic responses. Independent in name only the inter-relationship of these factors to each other and to the situation as a whole is so closely knit as to discourage separation (chart 1).

The individual responding to a strong emotional stimulus does so to a greater or lesser degree through the medium of these patterns. The amount of response will be in proportion to the adequacy or inadequacy of the whole. Thus the psychopath is characterized, as Kahn<sup>1</sup> has indicated, by a quantity rather than a quality reaction and his psychopathic tendencies measured through the mounting sum of his instability, excitability and anti-social tendencies. The *quality* of the response will on the other hand be colored and perhaps determined by the individual's *physiological* patterns.

Confronted with a difficult situation, individuals tend to respond by (1) either facing it and attempting to reach a solution—normal reaction, (2) by refusing to meet it and resorting to distractions, as a cover up—extraverted reaction, (3) by withdrawing within themselves—introverted reaction, (4) by taking refuge in ideas of persecution—paranoid reaction, or (5) by demonstrating such an exaggerated response that the original stimulus or

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situation is lost sight of—hysterical reaction. Combinations of these patterns in varying degrees are not infrequently observed although it is probably correct that one of them tends to predominate. This major pattern has been shown in many instances to possess a relationship to the physical build of the individual. Thus the asthenic leptosomic person often demonstrates introverted tendencies, the pyknic, extraverted ones and the athletic

### PHYSIOLOGICAL AND PSYCHOLOGICAL PATTERNS

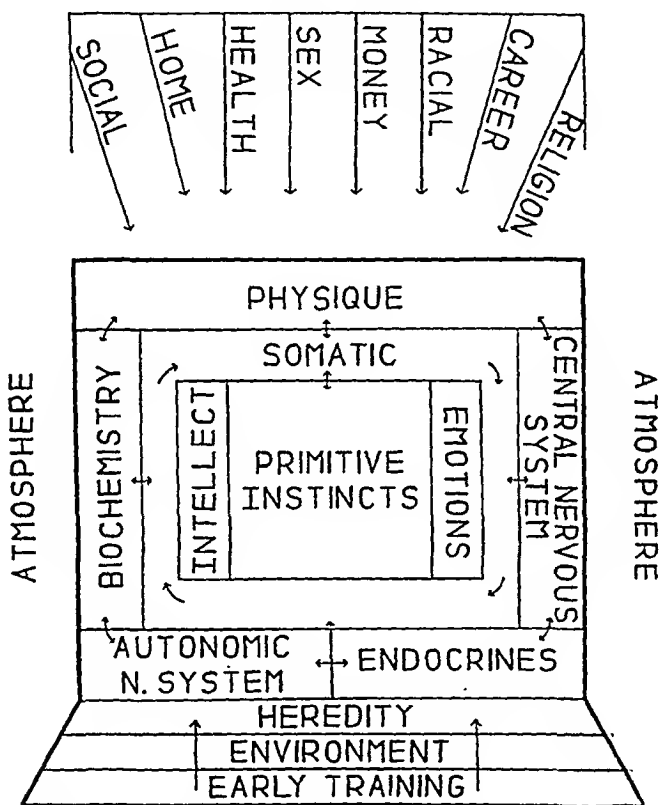


CHART 1. The heavy black line encloses the physiological and psychological patterns present in human beings. Disturbances or alterations in these, either alone or in combination with others may play a part in the adjustment of the total organism. Their inter-relationship is indicated by the arrows. Various situational factors are enumerated as well as the influence of barometric fluctuations, humidity, etc., which are grouped together under the term 'Atmosphere.'

type paranoid reactions. Psychological patterns may be conceived of as a framework from which a mental emotional response appropriate to the individual's make up, will be projected.

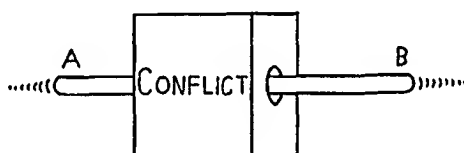
Consideration of these points brings into question the advisability or even the possibility of differentiating the organic response from the functional. Definitions fail to clarify the issue since we have no accurate means of determining when one reaction has ceased or another begun. Thus we



are aware that chronic anxiety states not infrequently result in somatic pathology, and that organic disease may be accompanied and in some cases overshadowed by emotional reactions. Conflicts may be expressed through physiological as well as psychological means, frequently through a mixture of the two (chart 2).

Recent advances in the fields of biochemistry and neural physiology point even further away from the functional—organic differentiation. Thus electroencephalographic tracings have demonstrated rhythmic disturbances in certain "functional" conditions,<sup>2</sup> shifts in the mitogenetic radiations of the blood have been reported in neurasthenic states<sup>3</sup> and an increasing number of publications call attention to organic changes in the diencephalon in autopsied 'functional psychoses.'<sup>4</sup>

<u>PHYSIOLOGICAL</u>	<u>PSYCHOLOGICAL</u>
BR ASTHMA	FRANK ANXIETY
PEPTIC ULCER	STATES
SP. COLITIS	DEPRESSIONS, etc.
ANGINA PECTORIS	



ENTIRE CONFLICT MAY BE  
EXPRESSED THROUGH EITHER  
A OR B OR THROUGH BOTH

CHART 2.

A stimulating article by Papez<sup>5</sup> considers an anatomical mechanism responsible in part at least for emotional elaboration. His theory proposes that "the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus and their interconnections constitute a harmonious mechanism which may elaborate the functions of central emotions as well as participate in emotional expression." Experimental work on animals together with clinical observations in the human lend support to this interesting conception.

In view of the increasing evidence for a biological conception of the psychoneuroses, it would appear that rigid distinctions between "functional" or "organic" are not only difficult but not without danger in that they tend to neglect the alternate consideration. Thus cases which are easily labelled hysteria may later demonstrate brain tumors, encephalitis, multiple sclerosis or other underlying pathology. In the presence of strong hysteroid mani-

festations it is not difficult to overlook or misinterpret neurological or physical signs. The problem more correctly resolves itself not into "*Is this functional or organic*" but rather "*How much is functional and how much organic.*" It is understood of course that "*much*" refers to an estimate rather than a strict evaluation.

The psychoneurosis may be viewed as a pathological expression of an inward conflict or as previously stated, an exhibition of maladjustment. It is not therefore a meaningless or tiresome reaction nor should it be interpreted as "*imagination*" or malingering. The latter constitutes a separate group possessing etiology and psychopathology peculiar to itself.

In the psychoneurosis the etiological conflict may or may not be known to the patient. Where it is known the reaction has been termed a *suppres-*

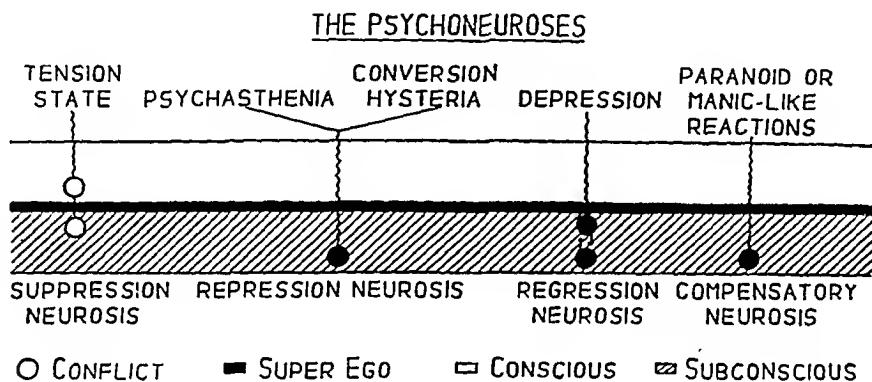


CHART 3. Four types of the more common neuroses are illustrated together with certain of their psychopathological aspects. When the individual is unaware of them the conflicts are shown deep in the subconscious mind. In the case of the suppression neurosis the conflict is indicated as lying in the conscious mind and "just below the surface" of the subconscious since here the individual is "vaguely to entirely aware" of its nature. The form in which the neuroses are presented to the outer world is illustrated in the top line as "Tension State," "Psychasthenia," etc.

*sion neurosis* (chart 3). Here the individual, though vaguely to entirely aware of the basic difficulty, is for some reason unable to express it fully *as such* and the suppression neurosis or psychoneurosis serves as the only means of outlet. Suppression neuroses are characterized physically by signs of increased tension. The syndrome which has been well outlined by Muncie<sup>6</sup> includes insomnia, "jittery" sensations, gastrointestinal disturbances, constriction headaches, palpitation, etc., all evidences of autonomic disturbance. Psychologically the patient presents an agitated depression.

*Clinical Example.* Mrs. A. B., aged 24, was referred because of the above physical symptoms which had developed within the past four months. Complete physical, neurological and laboratory studies revealed nothing of significance. The social history developed very little on first questioning. The patient insisted that her marriage of five years' duration had been entirely happy. She had never been pregnant but seemingly had no regrets. It was many weeks before the patient was willing to admit the significant conflict, namely that marital relations had never been consummated

due to impotence on the part of the husband. The patient had spent five years of frustrated sexual life subjected to many indignities by the husband who had threatened suicide if she ever discussed this. Her own sense of shame and inadequacy lent additional impetus for silence. The patient saw no possible connection between her physical symptoms and the marital conflict. Two years of treatment (which included divorce) have resulted in a good recovery. In this case the patient obviously was aware of the conflict but unwilling to admit it and unable to understand its outward manifestations.

There are on the other hand individuals who are entirely *unaware* of the etiological difficulty. These cases are termed *repression neuroses* or *psychoneuroses*. The unawareness may be the result of several factors: 1. The original psychic trauma is not infrequently one which occurred many years previously and the passage of time has served as a "cover up." 2. As Freud<sup>7</sup> has pointed out, at the time when the trauma occurred the patient was unable to find either adequate expression or a solution. 3. As a result of this, the difficulty was not faced but was thrust back into the subconscious mind where it gradually assumed different proportions through its association with other memories and conflicts. Difficulties which the individual seeks in this manner to bury and "forget" act as foreign bodies. Sooner or later their presence makes itself known, most frequently through physical symptoms acting as symbolic manifestations of the hidden conflict.

The repression neurosis expresses itself either in the form of phobias and compulsions (psychasthenia) or in the development of functional blindness, deafness, aphonia, paralysis, etc. (conversion hysteria). Physically the psychasthenic demonstrates tension symptoms, the conversion hysteria complaints referable to the region involved. Psychically the former group show agitation restricted for the most part to the dominant phobia. The conversion hysterics typically show *no evidence* of mental or emotional distress, the conflict being totally converted into and expressed through the blindness, paralysis, etc. Such patients are usually cheerful to the point of euphoria taking a hearty interest in their major "physical" complaint.

*Clinical Example.* 1. Psychasthenia. Mrs. T. E., aged 42, was referred because of a cancer phobia. The patient was an intelligent woman who had had nurses' training. Present complaint had developed two years previously when a hysterectomy had been performed for fibroids. Complete examination at this time and on numerous subsequent occasions had failed to reveal any evidence of malignancy. The patient, however, was convinced she had cancer. This she had variously located in the pelvis, the small intestine, the stomach and more recently the sacral spine. The patient was tense and agitated concerning her phobia and its effect on her future. At the end of a conference she was usually able to rationalize—even to laugh, about her 'moving malignancy,' but the next day the fear tended to recur. The patient characteristically would state that she knew the fear was groundless, that nevertheless she could not help it, that perhaps the doctors were mistaken or were not telling her the truth. Previous history demonstrated a tuberculosis phobia 20 years before. The patient denied any known conflict, evading, however, certain questions pertaining to her early home life and generally maintaining the attitude, 'I'm not a neurotic so I must have cancer.' Prolonged investigation brought to light a markedly hostile attitude toward

her mother whom she had always considered a 'nervous neurotic,' and whose numerous complaints irritated the patient excessively. Of late years the husband had been forced through business to spend an increasing period of time away from home. It became evident that the patient bitterly resented this though she had made no complaint. The cancer phobia therefore served a dual purpose: 1. If she had cancer she would be in a different category from the mother, in other words, 'really ill and not neurotic'; and, 2. If she had cancer her husband would be forced to stay home. This type of reasoning had, needless to say, never been indulged in by the patient and its gradual unfolding met with resistance. This patient has shown moderate improvement during two years' treatment, the cancer phobia being less constant.

*Clinical Example.* 2. Conversion Hysteria. M. B., aged 28, was referred because of paralysis of both legs. Present complaint was of three months' duration and had been sudden in onset. There was no physical or neurological history of significance. Complete examination including lumbar puncture and roentgen-rays of the spine was negative. The patient was calm and in no sense worried or apprehensive. During the examination she was overly anxious to help. Social history gradually developed the following picture—the patient had lived on a farm with two small sisters and her widowed father to whom she was deeply attached. One night 10 years previous to the onset of the present difficulty the father suffered a severe heart attack. Having no telephone and the car being out of order the patient rode a bicycle three miles to the nearest physician. By the time the doctor arrived the father was dead. The patient's grief was profound but financial worries became so pressing that for the next nine years she attempted to forget the whole picture, seeking feverish distraction in work. One month before the onset of the paralysis unexpected financial aid was received. The patient for the first time had an opportunity for leisure of a sort. Recollections of her father and his death became more acute. One morning she awoke unable to walk. Continued investigation gradually brought to light a pathological sense of guilt which the patient felt for her father's death. She had "not ridden fast enough," if she had "pedaled more rapidly the doctor would have arrived sooner" and her father would have been saved. It was therefore her fault that he had died. For obvious reasons the patient had been unwilling to contemplate this patricidal aspect. As the situation was slowly worked out she made a complete recovery. It is interesting that the legs, the principal offenders (in the ride to seek help) were the regions selected for "punishment" by the paralysis.

Another type of reaction is that which takes place in an individual who is also unaware of the nature of the etiological conflict but responds to its disguised manifestations by withdrawal or retreat. Such a picture is termed a regression neurosis. The person drawing within his shell presents to the outer world evidences of fatigue, anorexia, weight loss and general malaise. Psychically there is depression expressed in attitudes of indifference, listlessness, apathy or despair (suicidal attempts being not infrequent).

*Clinical Example.* Mr. W. A., aged 35, comes in because he feels vaguely unwell. Present complaint began three weeks previously. Physical examination and laboratory studies were negative. Social history revealed that the patient had suffered financial reverses during the past year but had accepted these with a considerable amount of stoicism until he discovered evidence that the reverses were in large part due to the dishonesty of his brother. Unable to accept or face what he felt to be an intolerable blot on the family honor the patient instead of pursuing the matter of settling it in one way or another withdrew into himself, became uncommunicative and listless and developed the picture outlined above. Psychotherapy was successful in establishing improvement.

Seeking relief from an unrecognized conflict through flighty-manic ideas, or through the projection of self hatred or ideas of persecution is termed a compensatory neurosis or psychoneurosis. Physically such individuals tend to have multiple complaints. Psychically their manner in the paranoid type is demanding, arrogant, suspicious and antagonistic; infantile, boisterous and exuberant in the manic patterns.

*Clinical Example.* Paranoid Type. N. Y., aged 26, white, unmarried male was referred because of difficulty in adjusting himself to his co-workers. An accompanying friend stated that Mr. Y. was becoming a problem in the office due to his overbearing actions. Physically the patient showed evidence of a pituitary gonadal dysfunction—hair growth scanty, feminine contour to hips, prostate smaller than usual. The external genitalia were normal and the testes descended. Psychologically the patient was overly sensitive, sarcastic and suspicious. After several conferences he admitted homosexual activities. Lately he had become fearful of discovery. His paranoid tendencies became exaggerated. His unwillingness to admit a sexual deviation led to a projection of his own ideas of hatred upon the outside world. He had begun to see in each person a potential enemy who was capable of surmising his secret. Feelings of inferiority and fear were compensated by a superiority complex. Psychotherapy and endocrine therapy (prephysin) were helpful in establishing a better mental attitude. There was no change in the glandular picture.

The present state of psychiatric terminology is so confusing that the clinician is not infrequently at a loss for a label. Actually a label is of far less usefulness than an understanding and evaluation of the underlying psychopathology. Summarizing this point certain generalities may be formulated:

1. That a psychoneurosis while constituting an exhibition of maladjustment is also paradoxically,

2. An *attempt* at adjustment. This becomes more evident when it is recalled that the psychoneurotic reaction provides an outlet through which conflicts may find expression. The use of such an outlet represents the patient's attempt to adjust.

3. The frequent involvement of the autonomic nervous system brings with it a train of symptoms which are eagerly seized upon by the patient. Thus tachycardia, anginal pains, increased or reversed peristalsis, peptic ulcers, spastic colitis, muscle tension, etc. become a respectable barrage through which the conflict finds socially acceptable expression.

4. The presence of these symptoms serves as a subconscious alibi for the patient. The man who is sick is excused and decisions, as Adler<sup>8</sup> has indicated, may be postponed.

5. Regardless of descriptive labels certain psycho-mechanisms tend to repeat themselves, and the recognition and evaluation of these appears of far greater significance than hair splitting distinctions between such descriptive prefixes as fatigue neurosis, neurasthenia, sexual, anxiety, occupational, situational, war or prison neurosis, etc. etc. These terms which serve as indications of the dominant symptoms tell us in reality little of the underlying pathology. Actually some 16 psycho-mechanisms are recognized. This

paper has considered four of the more common ones, suppression, repression, regression and compensation. Using this classification of Kempf's<sup>9</sup> the clinician seeks to estimate the degree in which each is present and its relation to future progress. Thus suppression neuroses tend to present a better prognosis than the other types—repression neuroses can usually be cleared of the immediate phobia or hysterical symptoms but there is a strong possibility that these may later be replaced by other fears or fixations. Regression neuroses considered here in only their mildest manifestations may be safely considered as potentially malignant. With their tendencies toward withdrawal, isolation, regression to childish levels, they offer a bizarre and unhealthy reaction. Compensatory neuroses tend on the whole to be benign, particularly the manic types, while paranoid expressions especially if accompanied by signs of disorganization and dissociation may be more serious. It is understood that these four types are not sharply demarcated, that it is quite possible to find evidences of a compensatory mechanism in what is quantitatively estimated to be, for example, a repression neurosis. In such cases prolonged observation coupled with clinical judgment must be relied upon.

No attempt can be made here to discuss the psychoses but attention should be called to a brief differentiation from the psychoneuroses.

1. A psychosis represents a *total failure* in adjustment whereas the psychoneurosis, as has been noted, is an *attempt* at adjustment.

2. A psychosis is a more serious problem than the psychoneurosis since in many cases mental deterioration occurs.

3. A psychosis is a total disorganization of the personality, the psychoneurosis a problem in maladjustment.

4. In a psychosis one finds *exaggerated* versions of the psycho-mechanisms discussed above. Thus compensatory mechanisms in their most extreme form are found in the manic type of manic depressive insanity (benign) and in paranoia (a malignant type of compensation). Regression mechanisms are seen in the depressed form of manic depressive insanity (benign), dementia praecox (malignant), where in the catatonic types, the patient demonstrates complete withdrawal.

The term malignant as employed here has reference to those conditions which show evidence of dissociation, disintegration and deterioration.

The *science* of psychotherapy is based upon three cardinal points: 1. Mental catharsis. 2. Desensitization. 3. Reëducation. The *art* of psychotherapy rests in the ability of the physician to fit these points to the individual case. It is the latter consideration which has been responsible for the accusations of vagueness which are often raised when the psychiatrist is asked to discuss therapeutic measures. It is difficult if not impossible to re-create the time spent with a patient, to present in review the conversation, attitude, mannerisms, etc. which were observed. Yet all of these are integral

parts of the procedure, the outcome of which rests upon the successful interpretation and evaluation of the *patient and his story*.

In a general way, however, after having obtained a detailed history several points may be mentioned:

1. The physician should have in mind several considerations:

- a. A careful physical examination properly to rule out demonstrable organic pathology.

- b. Bearing in mind that a psychoneurotic element may overshadow and for a time obscure physical disease, repeated physical examinations at different intervals may be indicated.

- c. Neurological examination. The possibility of brain tumor or encephalitis as a background calls for a neurological examination, especially ophthalmoscopic studies.

- d. Laboratory studies. Where possible serology, complete blood counts, and urine examinations are desirable. Occasionally a basal metabolic rate will be found to have variations from the normal, not infrequently on the hypothyroid side. Changes in blood sugar, calcium, cholesterol, vitamin A content, etc., while of great interest and frequent significance, call for more specialized assistance than is usually available.

The point originally mentioned, of a detailed history, needs further elaboration. During the history taking considerable information can be obtained from observation of the patient's manner, attitude, willingness or unwillingness to touch on certain aspects of the story, etc. Introverted, extraverted, paranoid and hysterical tendencies may be brought out during this time. Physical complaints no matter how bizarre should be later checked as noted above. The physician having obtained the available story and performed a physical examination will be wise to consider the possibility of a psychosis. The differentiation is not always easy; in general, however, certain points may be stressed:

1. A psychosis tends to show more exaggerated reactions than a psychoneurosis.

2. A psychosis often has attending organic pathology—toxic conditions, general paresis, menopause, arteriosclerosis, senility, etc.

3. A psychosis may demonstrate hallucinations, delusions, disorientation and dissociation.

In certain paranoid psychoses where mental deterioration occurs late if at all the problem may require hospital observation.

The first part of psychotherapy, i.e., mental catharsis, consists in encouraging the patient to tell his *entire story and in the way in which he chooses*. The time required will depend upon how much of the conflict is known to the patient and how willing and ready he may be to discuss it. As a minimum several weeks may be required before catharsis is effected, as a maximum, many months. It does not follow that the disclosure of the

etiological conflict is *always* the best therapy. In certain of the regression neuroses (depressions for example) the patient may not be able to adjust himself to the "complete view of the whole." Clinical judgment then is essential in determining in each case how far this first part of therapy should be pursued. Following the disclosure of the etiological conflict an attempt is made to secure desensitization through therapeutic conversations in which the patient is encouraged to look upon his difficulties from different points of view. The purpose of this is to develop perspective, objectiveness and an understanding of the manner in which the conflict developed and its methods of expression. Reëducation is then begun. The patient's future is considered in relation to his present abilities and potentialities. Changes in environment or manner of living may be necessary and advice on the prevention of other neurotic episodes is given. Reëducation of the family is included in this procedure as their sympathetic understanding and co-operation is necessary.

The use of drugs, especially sedatives, is frequently required. In our experience phenobarbital grains  $\frac{1}{4}$  t.i.d. or q.i.d. is a better choice than bromides<sup>10</sup> and has a distinct use in the treatment of tension states. Sodium amytal grains  $\dot{\text{i}}$  b.i.d. or t.i.d. may also be of benefit. For hypnotics nembutal grains  $\dot{\text{i}}\dot{\text{s}}\dot{\text{s}}$  or sodium barbital grains  $\bar{\text{v}}$  are recommended. For those unable to take the barbiturate hypnotics, paraldehyde drams  $\ddot{\text{ii}}$  is a good substitute.

In conclusion the question of therapy may be summarized in the following fashion:

1. An individual presenting a picture with psychoneurotic manifestations should be studied from a physical, neurological and when possible, a biochemical endocrine aspect as well as a psychiatric one.
2. If physical neurological or other demonstrable pathology is found this should be treated first.
3. Psychotherapy should be directed at (1) the disclosure of the etiological conflict, (2) the rationalization or desensitization to this conflict, (3) reëducation of the patient.
4. The possibility that one is dealing with a psychosis rather than a psychoneurosis should be carefully considered.

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# LUPUS ERYTHEMATOSUS DISSEMINATUS\*

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INCREASED attention has recently been drawn by various observers<sup>1-7</sup> to the importance of visceral involvement in acute lupus erythematosus. A greater familiarity with the signs and symptoms of this disease has naturally resulted in a more frequent recognition of this syndrome. Ludy and Carson<sup>8</sup> believe that the incidence has actually increased.

The exact diagnostic criteria have not yet been established, however. This is due not alone to the fact that the etiology is unknown but more so because there seems to be no minimum number of clinical or pathological features that one may expect to find consistently in each case. While cutaneous lesions, arthralgia, polyserositis, endocarditis and nephritis are the commonest attributes of this syndrome, any one or several of these may be absent. Nevertheless, the impression is gaining ground that this syndrome is actually one disease with a fairly clear-cut age and sex incidence, an intermittent course of several months or years, and an almost invariably fatal termination. In defending the entity of this disease one need hardly plead further than to cite rheumatic fever as a precedent.

We have studied a typical case of disseminated lupus erythematosus for 20 successive months from onset to termination. This case is somewhat unusual in that it presents a greater number of the well recognized clinical and morphological features of this disease than is usually encountered in any one single patient.

## CASE REPORT

*History:* Eleanor K., a white American girl of 20, first became ill in September 1937. Her past history was non-contributory. During the preceding summer she had been exposed to a good deal of sunlight on a camping trip and on weekly fishing trips in a sail boat. She stated that even on mild exposure she would develop a sunburn and with it unusual reactions consisting of severe headaches and repeated vomiting. Her illness began with migrating polyarthritides involving practically all the joints of the body and associated with a low-grade fever. This onset was not immediately preceded by exposure to sun. From September to Christmas the symptoms were mild enough to permit her to be up and about. On December 25 she began to vomit and continued to do so about twice daily for two weeks. This was accompanied by anorexia, weakness and mild diarrhea. She later noticed dyspnea, orthopnea, palpitation and precordial pain. One week before admission she developed a sore throat and a cough productive of a sputum which was occasionally blood streaked. During the fourth month of her illness and four days before admission, a skin eruption appeared on both cheeks. This was symmetrical, circumscribed and of a deep reddish-purple color. A physician told her she had erysipelas.

*First Admission:* The patient was admitted for the first time to the Third (New

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York University) Medical Division of Bellevue Hospital on January 15, 1938. She appeared acutely and seriously ill, prostrated, feverish, apathetic, dyspneic and orthopneic but not cyanotic. Over both cheeks and ear-lobes were symmetrical, circumscribed, intensely erythematous, superficial lesions covered with a fine scale. The skin over the bridge of the nose was clear. Superficial ulcerations with telangiectasia were present on the soft palate and uvula. The throat was acutely inflamed and the glands of the neck were palpable. Bilateral papilledema was present with superficial linear hemorrhages close to the disc; the retinal venules were slightly dilated and tortuous, but the arterioles appeared normal. The apical impulse of the heart was not palpable; the rhythm was regular and the rate 120 per minute. A presystolic gallop and a systolic blowing murmur were audible over apex and base.  $P_2$  was louder than  $A_2$ . Blood pressure was 120 systolic and 60 diastolic. The lungs and abdomen were negative. The neurological status was normal. The temperature was 104° F.

*Course:* From the fifth day to the beginning of the fifth week petechiae appeared in crops in both conjunctival sacs. On the sixth day a small ulcer developed over the coccyx which advanced rapidly and in the course of a week became an extensive deep necrotic bed sore about 2½ inches in diameter, progressing later to expose the spines of the sacrum and extending into the left ischial fossa. Toward the end of the second week the skin eruption and buccal mucous membrane lesions began to disappear. During the third week she suffered from attacks of paroxysmal dyspnea; no other signs of left ventricular failure were present and the lungs remained perfectly clear. The paroxysms disappeared once the patient was placed in an oxygen tent. She remained in the tent for five days and thereafter suffered no recurrences of dyspnea.

From the fourth through the ninth week the patient was incontinent of urine and feces and throughout the sixth week was comatose and irrational. Her temperature during this period varied between 100° and 105° F. At the beginning of the eighth week her general condition began to improve. She no longer was irrational. She was cheerful and interested in environment. She regained a desire for food. Her temperature, however, ranged between 100° and 103° F. and multiple abscesses appeared in the region of the bed sore. Despite the fact that she felt and appeared much improved, a to and fro pericardial friction rub was heard during the ninth week and persisted for 14 days. Throughout this interval no petechiae could be found and the electrocardiographic tracings (both standard and precordial leads) were within normal limits. With the friction rub an apical systolic blowing murmur and a presystolic gallop were heard.

By the eleventh week few abnormal findings were present. The temperature was normal. The bed sore began to heal rapidly. The cardiac findings were normal except for a rate of 100 per minute and an apical systolic blowing murmur. There were no petechiae. The papilledema and retinal hemorrhages were gone. The skin and mucous membrane were normal. The patient was no longer incontinent. During this week an abscess appeared over the left shoulder but cleared soon after aspiration. The patient had not menstruated for the past six months. She was discharged at the end of the eighteenth week (May 20) after having been up and about the wards with no complaints and no fever for two weeks.

*Therapy:* Treatment consisted of supportive measures. For the skin and mucous membrane lesions nicotinic acid was tried; 200 mg. a day were given for 10 days beginning January 26. During this period these lesions cleared considerably but they had begun to improve a few days before nicotinic acid was first given, and furthermore, despite this gain, the patient's general condition was growing steadily worse. She did not begin to recover until many weeks after nicotinic acid was discontinued.

Seven transfusions (500 c.c.) were given from the second to the tenth week and each time some clinical improvement was noticed for several days afterwards.

The diet was high in calories and vitamins. Fluids containing sodium chloride and glucose were given parenterally when the patient was unable to take food by

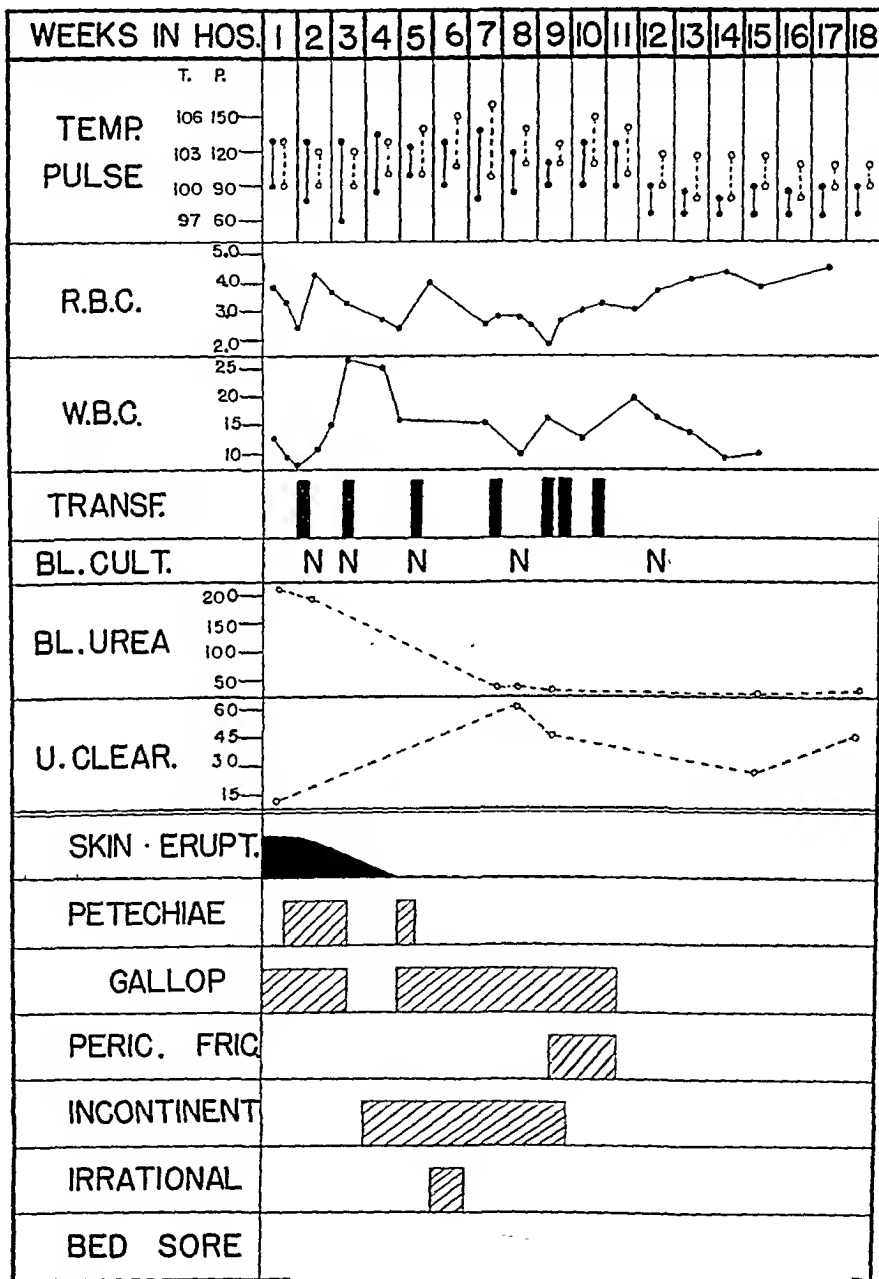


FIG. 1. Chart of the clinical course during first admission.

Hos. = hospital; Temp. = temperature designated in maximum and minimum readings by solid circles; Pulse = represented by open circles; R.B.C. = red blood cell count in millions per cu.mm.; W.B.C. = white blood cell count in thousands per cu.mm.; transf. = transfusions, each block represents 500 c.c.; bl. cult. = blood culture; N = negative; Bl. urea = blood urea in mg. per cent; U. clear. = urea clearance expressed in per cent of normal; peric. fric. = pericardial friction rub.



The urea clearance rose on the latter date to 59.7 per cent of normal. This is about the time that the specific gravity reached 1.020. On March 17, April 25 and May 20 the blood urea was 30.6 mg. per cent, 22 mg. per cent and 32.6 mg. per cent, respectively, and the urea clearance was 45 per cent, 28 per cent and 44 per cent of normal, respectively.

At no time did the blood pressure rise above 126 systolic or 80 diastolic.

*Bacteriological and Immunological Studies:* Blood cultures (aerobic and anaerobic) taken January 22, January 31, February 12, February 18 and April 2 were all sterile. Throat culture (January 18) showed numerous staphylococci and hemolytic streptococci. The culture from the bed sore (February 13) showed diphtheroids, hemolytic and non-hemolytic staphylococci and *B. Coli*. The pus aspirated from the abscess on the left shoulder (March 31) contained hemolytic staphylococci. The cervical smear showed no gram-negative cocci.

The Wassermann reaction was negative. The gonococcus complement fixation test was plus-minus. The antistreptolysin, antifibrinolysin, hemolytic streptococcus agglutinin and precipitin (Lancefield's "C" substance) titers done during the first week and last were within normal limits on both occasions.

*Hematological Studies:* The red blood cell count on admission was 3,900,000 and the hemoglobin 78 per cent (11.3 gm.). The white blood cell count was 12,650 with 57 per cent polymorphonuclears, 15 per cent lymphocytes, 16 per cent metamyelocytes II, 7 per cent metamyelocytes I and 5 per cent monocytes. Ten days later the red blood cell count fell to 2,420,000 and after a transfusion of 500 c.c., rose to 4,300,000. The anemia was most severe at the beginning of the ninth week when the red blood cell count was 1,800,000 and the hemoglobin 52 per cent (7.5 gm.). With the aid of three more transfusions and an anti-anemic diet, the erythrocytes gradually rose to 4,500,000 and the hemoglobin to 83 per cent (12.0 gm.). The white blood cell count at no time was below 7,300 and during the third week it reached a maximum of 29,600. Roentgenological examination of the lungs was normal. An azygos lobe was noted. The heart shadow was moderately enlarged.

*Electrocardiograms* taken on seven occasions were all within normal limits, showing either regular sinus rhythm or sinus tachycardia. There was no deviation of the electrical axis and no conduction defects.

*Porphyrin Studies:* Twenty-four hour urinary porphyrin excretion studies\* showed an output of 475 micrograms during the last week of the patient's hospital stay. Six subsequent determinations done a few weeks later showed, however, an excretion of only 35 micrograms per day.

*Second Admission:* The patient was seen again on September 14, 1938, four months after discharge. She had no complaints except mild joint pains and contraction of flexor tendons of the two last fingers of her right hand. She agreed to enter the hospital for further studies. Her weight had risen from 95 to 131 lbs.; blood pressure 120 systolic and 78 diastolic. The fundi were normal. Heart was normal except for a rate of 110 per minute. Electrocardiogram showed no abnormal changes except ventricular premature contractions. Skin was clear. Alopecia which had occurred soon after discharge was now undetectable. No petechiae could be seen. The red blood cell count was 4,430,000 with 75 per cent hemoglobin (11.0 gm.). The white blood cell count was 5,900 with a normal differential. The platelet count was 124,040. An Addis urine sediment count at this time showed: specific gravity 1.021; pH of 6.8; albumin ++; red blood cell count 11,870,000; white blood cell count 6,740,000 and casts 973,000. The blood urea was 24.4 mg. per cent and the

\* Normal porphyrin excretion in the urine varies from 0 to about 100 micrograms per 24 hours. The porphyrins were extracted by the ether-acetic acid-hydrochloric acid method of Fischer and determined as coproporphyrin by comparisons with standard solutions of coproporphyrin spectroscopically and fluorimetrically. The determinations above reported were done by Dr. L. A. Rosenblum.

urea clearance was 75 per cent of normal. The levulose tolerance test and bromsulphalein test showed perfectly normal liver function. Thus, clinically the patient was found markedly improved, though a severe microscopic hematuria persisted. She left the hospital in four days.

*Third Admission:* During the month of October 1938, she suffered with multiple joint pains and weakness and noted several ecchymotic areas on her skin. There was no bleeding from any of the mucous membranes. On the morning of November 10 she was seized with a sudden, severe, lower abdominal, cramp-like pain followed by nausea and vomiting. She was told by a physician that she had acute appendicitis. On admission to Bellevue Hospital that night there was resistance but no true rigidity over the right lower quadrant, with considerable rebound tenderness. Pelvic examination was negative except for tenderness upon moving the uterus. Several small ecchymotic areas were present over thighs and legs. The right knee and wrist were warm and tender. The cardiac impulse was not palpable, the rate was 134 and a loud systolic blow was heard at the apex. There was no friction rub or gallop. The eye grounds were normal. There were no petechiae, no rash, no splenomegaly or hepatomegaly. The abdominal pain soon subsided but fever and occasional vomiting continued and anemia progressed. Two weeks after admission she developed acute pharyngitis with sudden rise in temperature to 104°. Throat culture showed diphtheria bacilli. Schick test was positive and the control was negative. Since the organisms could not be recovered on successive cultures and since there were no clinical signs of diphtheria, no anti-toxin was given. A week later the temperature again was normal and the patient comparatively free of symptoms for two weeks.

During the sixth week she became seriously ill, cyanotic and dyspneic, and there appeared frank signs of consolidation first in the entire left lung and then in both bases. The temperature rose to 104.6° and the leukocyte count to 56,000. No chill or bloody sputum was present and the cough was unproductive. A throat culture yielded unclassifiable pneumococci so that no specific anti-serum could be given. She did not respond to customary doses of sulfanilamide or sulfapyridine, with blood concentration of free sulfanilamide as high as 11 mg. per cent. She was put in an oxygen tent and after a stormy period of two weeks, during which time she was once again irrational and incontinent, a moderate improvement was observed. The signs of consolidation shifted from one lung to the other during the course of the next few weeks. Severe chest pain now became a prominent symptom and bilateral pleural effusion was noted. Five hundred c.c. of serosanguinous fluid were removed from the right chest during the ninth week and a few days later another paracentesis yielded 350 c.c. No organisms were recovered on culture. The chest signs slowly disappeared and the lungs remained clear for five weeks, when signs of consolidation and fluid re-appeared.

At about this time arthralgia recurred, peripheral edema developed and the liver became palpable. The edema became progressively more severe, was of generalized distribution but most prominent in legs and feet. The liver edge descended to three fingers-breadth below the costal margin. The spleen was not palpable. Conjunctival petechiae re-appeared and on several occasions some observers felt convinced they heard a diastolic rumbling murmur at the apex. A presystolic gallop was present intermittently. Furuncles and subcutaneous abscesses appeared on her back and face. The former bed sore again became extensive. The original butterfly erythematous eruption of the face re-appeared for four weeks towards the end of the course and then faded completely. During this time the optic disc margins again became blurred, but no hemorrhages or exudate were present. First muscle twitches appeared and later she had two generalized tonic convulsions with no localizing or residual signs. Examination of spinal fluid was negative. The major therapeutic problems consisted of combating unyielding anorexia, nausea and vomiting, and a resistant anemia, which failed to respond to a total of 10,000 c.c. of whole blood. Save for a few days of

comparative improvement scattered through 25 weeks of prostrating and wasting illness, the patient continued to lose ground steadily. During the last few days she was irrational and incontinent and complained of chest pain and dyspnea. The bed sore became very extensive, edema increased and now included the face. The abdomen was distended and was thought to contain free fluid in the peritoneal cavity. Tachycardia and gallop were present. The patient died on May 1, 1939, 20 months after the onset of her illness.

*Renal Studies:* The urea clearance on November 16, 1938, was 30.4 per cent of normal and blood urea was 75.4 mg. per cent. The non-protein nitrogen steadily decreased as follows: December 27—60 mg. per cent; January 18—32 mg. per cent; February 6—33 mg. per cent; March 23—40 mg. per cent; and April 21—38 mg. per cent. An Addis sediment count of the urine, done on November 16, 1938, showed 7,665,000 red blood cells, 465,000,000 white blood cells and 26,000 casts. Fifty-four

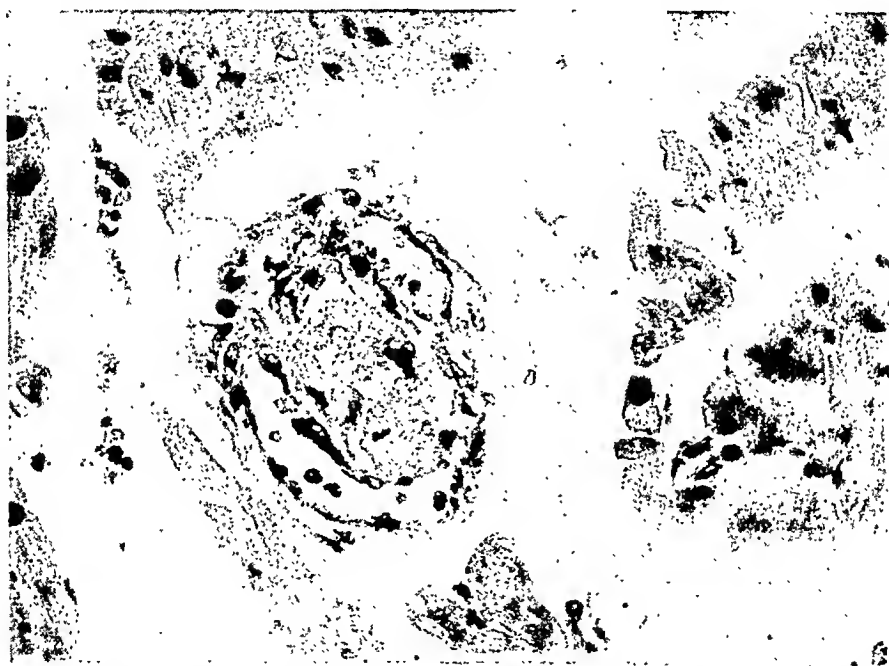


FIG. 3. Photomicrograph (high power magnification) of a section through left ventricular myocardium showing canalyzing thrombotic lesion in a myocardial vessel. The thrombus was composed of granular, pale eosinophilic material lined by endothelial cells.

urinalyses done during this admission showed a specific gravity ranging between 1.006 and 1.020, a persistent proteinuria varying from one to three plus, a few red blood cells and numerous white blood cells per high power field in each specimen. At no time did the blood pressure rise above 150 systolic and 80 diastolic. The average reading was 120 systolic and 60 diastolic.

*Bacteriological and Immunological Studies:* Blood cultures taken during the third, fourth, sixth and eighth weeks were sterile. As mentioned above, the throat culture on November 23 showed diphtheria bacilli but these could not be recovered on subsequent cultures. From a subcutaneous abscess and facial furuncle *Staphylococcus aureus* was grown. The pleural fluid of January 14, 1939 was sterile, as was the spinal fluid of April 9, 1939.

The Wassermann reaction was negative. The gonococcus complement fixation test was negative. The antistreptolysin, antifibrinolysin and hemolytic streptococcus



agglutinin and precipitin titers done March 19, 1939 were again within normal limits. The Schick test was positive. The colloidal gold curve of spinal fluid was 000 000 0000.

*Hematological Studies:* The red blood cell count varied between 4,200,000 and 2,100,000, remaining between two and three million in most instances and rising above three million only after one or two transfusions. The hemoglobin ranged between 5.8 and 10.0 gm. per 100 c.c. The white blood count was elevated from the third to twelfth weeks, during the period of pulmonary infection and high fever. Leukocytosis on one occasion reached 56,200, on another 46,200, and on a third 42,650 with an increase in polymorphonuclears and metamyelocytes. During the latter half of her course the white blood count stayed between five and ten thousand with a normal differential. At no time was leukopenia present. The erythrocyte sedimentation rate was elevated.

*Roentgen Examinations:* The lungs on January 17, 1939, showed bilateral pleural effusion reaching on the left side as high as the subapical region and on the right, filling the lower two-thirds of the chest. There was also a moderate amount of pneumonitis visible in the areas not obliterated by the effusion. As before, the azygos lobe was noted. On April 14, 1939, extensive broncho-pneumonic infiltration was seen in both lung fields.

*Electrocardiograms:* The tracings which were normal during the first admission and during the first month of this admission showed persistent low voltage during the last two months of life. Tachycardia and premature ventricular and His bundle contractions were the only other abnormalities. There was no deviation of the electrical axis and no prolongation of P-R interval or QRS complex.

*Autopsy:* Autopsy was performed two hours after death, by Dr. Eugene Clark.

Macroscopic examination: Except for several furuncles on both cheeks there were no facial lesions. Decubitus ulcers were present over the sacrum and both iliac crests. On opening the peritoneal cavity, approximately 3500 c.c. of clear light yellow fluid escaped. Delicate fibrous and fibrinous adhesions extended from the omentum, large bowel and stomach to the anterior abdominal wall. Almost the entire free surfaces of both liver and spleen were covered by similar fibrinous exudate and fibrous adhesions measuring 2 cm. in thickness. The liver extended 3 cm. beneath the costal margin.

On opening the chest, both pleural cavities were found to be completely obliterated by organizing fibrinous exudate about  $2\frac{1}{2}$  cm. thick. Similar adhesions were present between the pleural and pericardial surfaces.

The heart weighed 580 grams. The pericardial sac was completely obliterated by fibrous adhesions. The right auricle and ventricle, and the tricuspid and pulmonary valves were normal. The left auricular endocardium appeared diffusely thickened, and pearly gray in color. The mitral ring showed a minimal degree of stenosis and admitted the tips of two fingers with difficulty. Both mitral leaflets were moderately thickened. On the auricular surface of the free borders of the posterior leaflet were small verrucous structures measuring 1 to 2 mm. in diameter. They were friable and light red in color. Extending over the entire ventricular surface of this leaflet was a large vegetation 5 mm. thick. It was dark red, granular and fairly friable, and partly obliterated the pocket between the cusp and subjacent endocardium. It extended downward along the endocardium of the posterior wall of the left ventricle for a distance of 2 cm. The anterior mitral leaflet was sclerosed and contained a small calcified deposit in its depth. It was free of any vegetations that could be seen grossly. The chordae tendineae were slightly thicker and shorter than normal. The left ventricle was moderately hypertrophied; its wall was 14 mm. thick. The myocardium, aortic valve, supra-valvular aorta and coronary arteries were normal.

The aorta was normal save for a few, light yellow, subintimal flecks in descending and abdominal portions.

The lungs were crepitant throughout. There were no areas of consolidation. A few small alveolar hemorrhages were noted in the right lower lobe.

The spleen weighed 510 grams. Its capsule was covered by loosely adherent fibrinous exudate  $2\frac{1}{2}$  cm. thick. The cut surface was deep red, with abundant pulp.

The stomach, intestines, pancreas and adrenals showed no noteworthy changes.

The liver weighed 1920 grams. Its free surface was covered by a fibrinous exudate similar to that covering the spleen. The cut surface was brownish red and the central veins were prominent. The gall bladder was normal.

There was a conspicuous inequality in the size of both kidneys; the left weighed 340 grams and the right weighed 120 grams. The capsule of the left stripped with

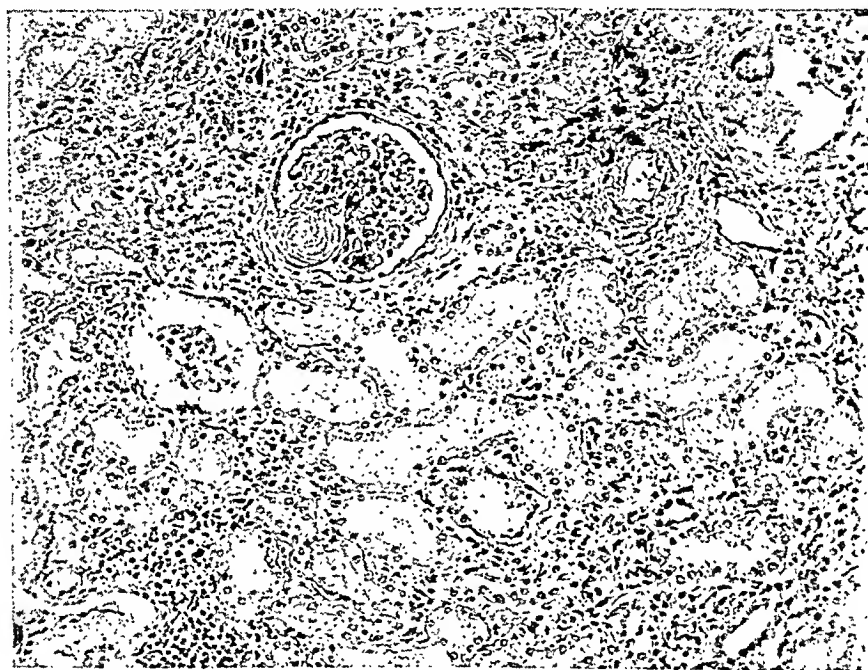


FIG. 4. Photomicrograph (low power magnification) of a section through right kidney showing healed focal lesion in the glomerulus like that seen in ordinary embolic glomerular nephritis.

ease, the surface was mottled, grayish yellow, and red because of small areas of congestion. The organ was softer than usual and on section the cortex was paler and wider than normal. The capsule of the right kidney stripped with some difficulty. The surface was pale reddish-gray and bore several linear cortical scars. The intervening surface between the scars was finely granular; the individual granules measured 1 mm. in diameter. On section, the cortex was markedly diminished in size and the cortico-medullary junction was indistinct. A slight degree of hydro-nephrosis with atrophy of the pyramids was noted but no ureteral obstruction could be found.

The bladder was normal except for a few small mucosal hemorrhages measuring 2 to 3 mm. in diameter.

The uterus, fallopian tubes and right ovary were normal. The left ovary contained a corpus hemorrhagicum measuring 1 cm. in diameter.

The peri-pancreatic lymph nodes were slightly enlarged, measuring 1 by  $\frac{1}{2}$  cm.

They were soft in consistency and the surface and cut section were pinkish gray in color. The remaining lymph nodes were normal.

The bone marrow of the vertebral bodies was normal. The remaining structures showed no significant changes. The brain was not examined.

Culture of the vegetations on the mitral valve revealed hemolytic streptococci.

*Microscopic Examination:* Heart: The posterior mitral leaflet was markedly and diffusely thickened by cellular granulation and fibrous tissue. There was extensive vascularization throughout its entire length and the vessels appeared as thick-walled arterioles in some regions but more often as young proliferating capillaries. There was an extensive proliferation of the histiocytes and a fairly dense focal infiltration of lymphocytes and polymorphonuclear leukocytes. There were many large hemosiderin-containing macrophages throughout the leaflet. The proximal three-fourths of the auricular aspect was lined by endothelium but the remainder as well as the entire ventricular aspect of the leaflet was the site of a homogeneous fibrinous vegetation which was continuous with the vegetation on the mural endocardium of the posterior wall of the left ventricle. The fibrinous vegetation appeared invaded by histiocytes and capillaries and showed very few polymorphonuclear leukocytes. There was fusion of the proximal portion of the ventricular aspect of the leaflet to the subjacent mural ventricular endocardium. This fusion appeared to be of firm fibrous nature and a similar union had occurred between many chordae tendineae and the ventricular surface of the leaflet as well as with the mural endocardium of the left ventricle behind the posterior mitral leaflet. There was no sclerosis or vascularization of the mitral ring. The endocardium of the left auricle showed no inflammatory changes. The anterior mitral leaflet showed alterations similar to that described in the posterior leaflet although on a smaller scale, including the fibrous cohesion of several chordae tendineae on the ventricular aspect. There were several large bacterial masses situated rather deeply in the leaflet though none were found on the fibrinous vegetation. In the leaflet itself polymorphonuclear leukocytes were fairly numerous.

The mural endocardium of the posterior left ventricular wall showed alterations similar to those found within the anterior and posterior leaflets; it did not extend beneath the elastic layers of the endocardium which were only slightly reduplicated. The endocardium was thickened to a degree which achieved a width of several mm. and the thickening was attributable to cellular granulation tissue well vascularized by thick-walled vessels and young capillaries on which was deposited a broad layer of homogeneous fibrin. Fused chordae tendineae could be very distinctly identified in this thickened endocardium.

The pericardium showed an extensive union with the epicardium by very vascular, loose, fairly cellular areolar tissue. There were thick-walled vessels in these fibrous adhesions as well as young capillaries. In a few places the adhesions between the serous membranes were of a homogeneous fibrinous character.

The myocardium beneath the mural endocarditis of the posterior left ventricular wall showed considerable fiber atrophy with interfibrillar fibrosis. Elsewhere the fibers showed a mild degree of nuclear and fiber hypertrophy. A few foci were encountered of sub-miliary size, consisting of a centrally placed capillary or arteriole plugged by bacterial masses with a surrounding zone of polymorphonuclear leukocytic infiltration and muscle necrosis. There were no Aschoff bodies or any structures even remotely resembling the latter. The larger and medium sized coronary arteries appeared normal. There was no perivascular fibrosis. There were a few small arteries and arterioles situated in the muscle subjacent to the mural vegetations in which definite intimal hypertrophy and medial fibrosis could be identified. A significant vascular alteration was found in thin-walled sinusoidal-like structures situated in the interfascicular connective tissue. These structures frequently con-

tained granular, pale, eosinophilic material, relatively acellular, surrounded by proliferating histiocytes and endothelial cells, practically occluding the lumen in many instances (figure 3).

Kidneys: Sections through the right kidney presented a uniform picture. The most striking alteration was that of extensive patchy tubular atrophy and interstitial fibrosis with condensation of glomeruli. In these patchy zones of atrophy, the most common glomerular lesion encountered was that of diffuse or partial hyalinization and atrophy, but within these areas, as well as in less altered portions of this kidney,



FIG. 5. Eleanor K., January 20, 1938. Eleanor K., May 18, 1938.

there were glomerular lesions of various other types. There were no glomeruli which appeared entirely normal. Many showed hyalinization of the so-called "focal embolic" type (figure 4), i.e., there was circumscribed hyalinization of a segment of the tuft with the remainder of the tuft showing only slight thickening of the basement membrane. These lesions appeared old and none showed evidence of recent necrosis. Other glomeruli showed a mild or moderate diffuse thickening of the capillary basement membrane with fusion of loops and simplification of the tuft. Many glomeruli showed synechiae between the tuft and the capsule. No crescents were seen but some glomeruli showed crescentic fibrosis. Many showed fibrous thickening of Bowman's capsule.

The tubules had disappeared in the large atrophic areas, elsewhere showed no alteration other than that of a focal calcification which involved collecting tubules chiefly. There was a moderate number of hyaline casts in the tubules. The interstitial tissue showed a diffuse fibrosis though the latter was more marked in the patchy zones of extreme atrophy. It was very densely infiltrated by lymphocytes and plasma cells.

The afferent glomerular arterioles and the interlobular arteries appeared entirely normal. There was, however, a severe focal lesion in the interlobar and arcuate arteries. A large number of these vessels showed partial or complete obliteration of the lumen by firm connective tissue in the intima which frequently showed capillarization. The internal elastic membrane was notably unaltered and the media and periarterial tissue appeared entirely normal in such lesions. This was, however, a focal process and more than half of the vessels of this size encountered in the sections appeared unaltered.

The mucous membrane of the pelvis and calyces showed a dense sub-epithelial infiltration of lymphocytes and plasma cells, and in some sections the calyx was full of pus.

The left or large kidney showed alterations of the glomeruli similar to that seen in the right. There was, however, a notable difference, in the absence of any extensive patchy atrophy or interstitial fibrosis. The process in this kidney was more diffuse and the interstitial scarring was less marked. The other difference appeared in the absence of any vascular lesion whatsoever, the arcuate and interlobar arteries in sections from this kidney appearing entirely normal. The pelvic mucous membrane showed the same inflammatory changes as noted in the right kidney.

Lungs: In all sections the pleural surfaces were thickened by fibrous exudate containing capillaries lined with thick cuboidal endothelial cells. The parenchyma showed a moderate degree of chronic passive congestion. One section contained several foci of organizing pneumonitis. Many of the smaller bronchi exhibited thickened fibrosed walls with foci of lymphocytes in their depths.

Spleen: The capsule was thickened in several areas by old fibrous connective tissue. The pulp was moderately congested and contained an excess of polymorphonuclear leukocytes. The follicular arterioles showed moderate intimal thickening of a hyaline nature.

Pancreas: The acinar and islet cells were normal. There was a moderate degree of diffuse inter- and intra-lobular fibrosis with atrophy of many of the glandular lobules. The thickened interlobular septa were infiltrated with moderate numbers of lymphocytes and fibroblasts. Scattered capillaries and venules exhibited partial or complete occlusion by hyaline masses, some of which were partially organized. The arteries were normal.

Liver: The capsule was normal but was covered by a very thin layer of delicate connective tissue strands. The central zone sinusoids were dilated with consequent atrophy of the surrounding polygonal cells. Many of the hepatic cells throughout the sections contained large lipoidal globules. The larger arteries exhibited slight intimal thickening by fibrous proliferation. The smaller vessels were normal.

Adrenal: The capsule was thickened by young fibrous connective tissue. A few of the capsular arterioles showed intimal proliferation, hyaline and fibrinoid degeneration of their walls with consequent narrowing of the lumen. The remaining portions of the adrenal gland were normal.

Bone marrow: The bone marrow of the vertebral bodies showed hyperplasia of the cells of the granulocytic series.

The remaining organs showed no unusual changes.

*Final Pathologic Diagnosis:* Chronic polyserositis (pleuritis, pericarditis, perihepatitis, perisplenitis) with ascites; chronic passive congestion of the lungs and

liver; chronic active mitral and left ventricular mural endocarditis of the atypical verrucous type with superimposed acute bacterial (hemolytic streptococcus) endocarditis; chronic glomerular nephritis of the diffuse and focal embolic type; focal endarteritis obliterans of the right kidney with patchy ischemic atrophy; chronic bilateral pyelonephritis; chronic interstitial pancreatitis with capillary fibrinous thrombosis and lymphadenitis of the peri-pancreatic nodes.

### DISCUSSION

In 1924, Libman and Sacks<sup>9</sup> described what they considered a distinct clinical syndrome associated with characteristic mural and valvular atypical verrucous endocarditis. Two of the four patients originally described by these authors had lupus erythematosus. In 1932, Gross<sup>10</sup> reported seven cases of Libman-Sacks disease; cutaneous lesions were present in three. In 1935, Baehr, Klemperer and Schiffrin<sup>2</sup> reported 23 cases of fatal lupus erythematosus with autopsy findings. Five of these had endocarditis of the atypical verrucous type. Keil quotes the late Dr. Louis Gross as having been of the opinion that from 30 to 50 per cent of the cases of lupus erythematosus demonstrate this endocardial lesion. It seems then that patients with lupus erythematosus may or may not have atypical verrucous endocarditis and conversely patients with this unusual type of endocarditis may or may not have lupus erythematosus. Our patient had both the cutaneous and endocardial lesions. The superimposed bacterial endocarditis reported here is rare but has been noted by other observers and occurs quite late in the course of the disease.

Studies of renal function have been reported in only a few of the cases that appear in the literature. Keith and Rowntree<sup>11</sup> found that renal function as tested by phenolsulphonephthalein excretion, by the level of nitrogenous bodies in the blood and by the ability to dilute and concentrate the urine was unimpaired as a rule. Rose and Goldberg<sup>8</sup> found that in two of their cases the function as judged by urea clearances was normal; neither of these two patients had azotemia. Nine of the 23 patients reported by Baehr, Klemperer and Schiffrin had azotemia and showed fixation of specific gravity of the urine. It is interesting that our patient showed first a marked impairment in renal function; i.e., a fixed specific gravity, a urea clearance which was 13 per cent of normal and a blood urea content of 217 mg. per cent, and then regained her capacity to concentrate urine and to clear urea (75 per cent of normal), thereby reducing her blood urea to a normal level. Even more striking is the fact that uremia, which in this disease is usually terminal, was followed by remission. In the latter phase of the patient's illness the urea clearance was again seriously reduced, though the blood non-protein nitrogen during the last week of life was only 38 mg. per cent. Albuminuria and hematuria persisted practically throughout the patient's course, even when she was symptom-free and apparently in remission. As is the rule in these cases, hypertension was absent. As one follows the course of lupus erythematosus from its onset, it becomes evident that the

degree of renal function impairment may vary from time to time and may not be unremittingly progressive. This may explain, in part, the wide variation in the reported results of kidney function tests in this disease.

It is noteworthy that the customary leukopenia was not observed in this case. In fact leukocytosis was present through the major part of the course, reaching a maximum of 56,200 white blood cells. At autopsy the bone marrow was found hyperplastic, largely because of an increase in the cells of the granulocytic series.

Baehr, Klemperer and Schiffrin are of the impression that those patients with erythematous lupus who are photosensitive, develop this disease or an exacerbation immediately after exposure to sunlight. Keil<sup>12</sup> disagrees with this observation. The case here reported demonstrates that while the patient was unquestionably sensitive to sunlight, exposure to sun did not immediately precede the onset of her illness nor the later appearance of the cutaneous manifestations. The skin eruption appeared several months after the other symptoms began, during which period the patient had remained indoors.

At autopsy the kidneys showed both diffuse and focal glomerular nephritis. Baehr et al. described glomerular lesions in 18 of 23 cases. Rose and Pillsbury<sup>6</sup> found them in all of the five cases autopsied and Reifenstein et al.<sup>7</sup> reported glomerular nephritis in 9 of the 17 cases collected from the literature.

An unusual feature in our case was the marked inequality in the size of both kidneys, one being almost three times as large as the other. It is noteworthy that many arteries of the smaller kidney were occluded, partially or completely, by severe intimal fibrosis. The internal elastic membrane and the remaining layers of these vessels remained unaltered. Such changes were conspicuously absent in the larger kidney. The "wire loop" lesions emphasized by Baehr and his co-workers were not found in this case.

The smaller systemic arteries, arterioles, venules and capillaries were widely affected. In most instances the changes consisted of intimal proliferation and fibrosis, in some the walls showed degenerative changes and in many the lumen was narrowed or occluded by thrombus formation. Such alterations were noted to a greater extent in the heart and kidneys and to a smaller degree in the spleen, pancreas, liver and adrenals.

The morphological changes in the heart conformed closely to the descriptions of Libman and Sacks and Gross.

#### SUMMARY

A case of lupus erythematosus with visceral involvement is reported. It is unusual in that so many of the multiple features of this disease were observed in one patient.

The clinical attributes consisted of photosensitivity, cutaneous eruption, alopecia, arthritis, pericarditis, endocarditis, petechiae, papilledema, pleuritis, pneumonitis, nephritis, transient uremia, splenomegaly, hepatomegaly,

ascites, peripheral edema, gastrointestinal disturbances, prolonged fever, anemia, leukocytosis, delirium, convulsions and coma.

The significant morphological changes consisted of atypical verrucous endocarditis (Libman-Sacks) with superimposed acute bacterial endocarditis, adhesive pericarditis, disseminated vascular lesions, polyserositis, focal and diffuse glomerular nephritis and interstitial pancreatitis.

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# THE RESPIRATORY AND THE CIRCULATORY SYSTEM IN FEMALES WITH OVARIAN DYSFUNCTION\*

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SOME women pass through the climacterium asymptotically, whereas others have innumerable complaints. Frequently symptoms do not cause undue annoyance and may be elicited only by careful questioning. In other cases they are so tormenting that medical treatment, bed rest, and even hospitalization may become necessary.

Opinion varies in regard to the incidence of symptoms. Some estimate it as high as 75 per cent of all women<sup>11, 12</sup> while others report 91 per cent or even more.<sup>30</sup> The marked difference in the intensity and frequency of symptoms seems to depend upon constitutional and endocrine factors and the status of the vegetative nervous system. Furthermore, the social position of the patient may play a rôle. One meets patients with climacteric symptoms much more frequently in private than in institutional practice. In the private practice of a cardiologist 22 per cent of female patients seeking advice had complaints caused by the disturbance of the activity of the ovarian glands.

It has been known for years that an arthritis or a psychosis (involutional melancholia) may be associated with the climacterium, and substitution therapy with ovarian hormones has been recommended. But even the relation of these conditions to the activity of the ovarian glands occasionally has been questioned and even denied until recently.

With regard to the sensations produced by disturbances of the circulatory system, it is generally appreciated that "hot flashes" and palpitation are common findings during, and caused by, the menopause. But these symptoms and others, which are discussed later, are usually regarded mainly as the consequence of a "climacteric neurosis" rather than of an actual illness. More recent investigations seem to prove, however, that these patients are actually ill and not merely neurotic. They indicate that the practical importance of the circulatory disturbances in climacteric females has been greatly underestimated.

## SYMPTOMS AND SIGNS

In a typical case the diagnosis is possible by merely obtaining the history from the patient. Most of the patients exhibit increased excitability and show an emotional instability and great nervousness. They weep readily and are greatly depressed. Others, however, enumerate their symptoms with great tranquillity.

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In the foreground are the "hot flashes" which are found in approximately 62 per cent of the cases.<sup>12</sup> Some authors, however, note them so regularly that they hesitate to diagnose the climacterium unless this symptom is present. Sweating, vertigo and a splitting headache are common.

Palpitation, cardiac pain and dyspnea constitute a syndrome encountered very frequently in patients with an organic heart lesion; but the same triad is also found with equal regularity in the climacteric female. More exact inquiry, however, often adds many important details. The palpitation does not present the characteristic features noted in paroxysmal tachycardia or of palpitation associated with organic heart lesions. It comes without apparent cause, frequently at night, and lasts only a few minutes. The pain is felt in the region of the cardiac apex or in the left parasternal region in the second or third interspace. This area is frequently hypersensitive to pres-

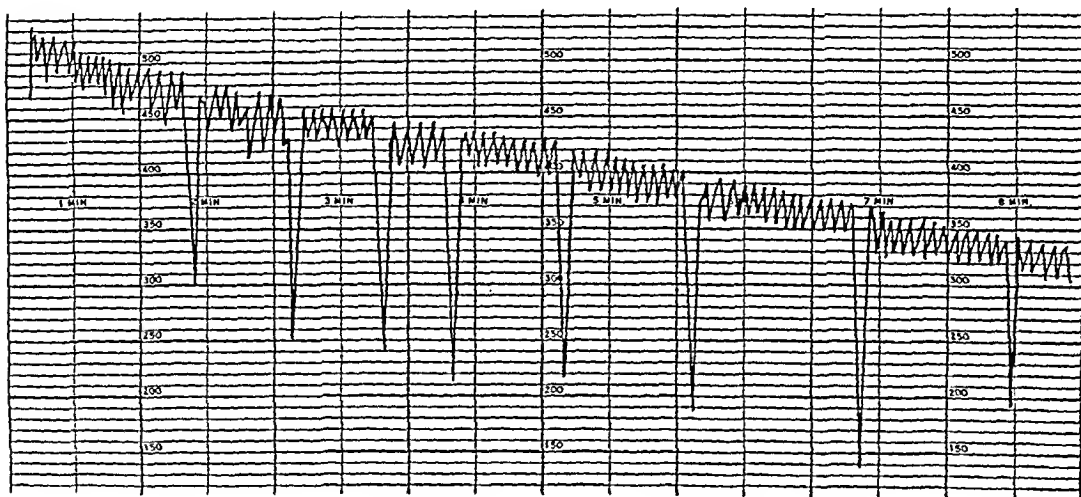


FIG. 1. Sighing respiration in a climacteric patient.

sure. Moreover, the pain may radiate "typically" to the left shoulder and down the left arm. It usually lasts but a few minutes, and is very similar to the pain found in myocarditis. Nitroglycerin may relieve.

The dyspnea of this group of patients presents features which are very suggestive of the correct diagnosis. It occurs independently of effort and may be present when the patient is resting quietly. Simple observation and careful questioning reveal that the dyspnea consists merely of single deep sighing respirations which recur at rather short intervals. Some relief of the oppression is thus afforded. Rarely is the patient aware of the true character of the respiratory disturbance, and therefore she mentions only the subjective feeling of dyspnea. When informed by the physician concerning the character of the breathing she recognizes immediately the sighing as such. This form of respiration is so typical that it readily permits the diagnosis.

Figure 1 shows the basal metabolism tracing of a 38 year old patient in the menopause, who complained of dyspnea and palpitation. The deep sighing respirations occurred once or twice every minute and are clearly visible. One will also notice that the deep respirations are not preceded by more superficial excursions, i.e., they do not have compensatory character.

Figure 2 shows the rather slow respiration of another patient, 54 years of age, who complained of dyspnea, palpitation, pain in the cardiac region and "hot flashes." In this instance as well the deep sighing occurred at least once every minute combined with an irregular and slow respiration. In both cases the disturbance of the respiration was very obvious during the examination. The basal metabolic rate in the two patients was —7.6 and —6.4 respectively. Both present quite typical instances of the two main varieties of the sighing respiration encountered in these patients.

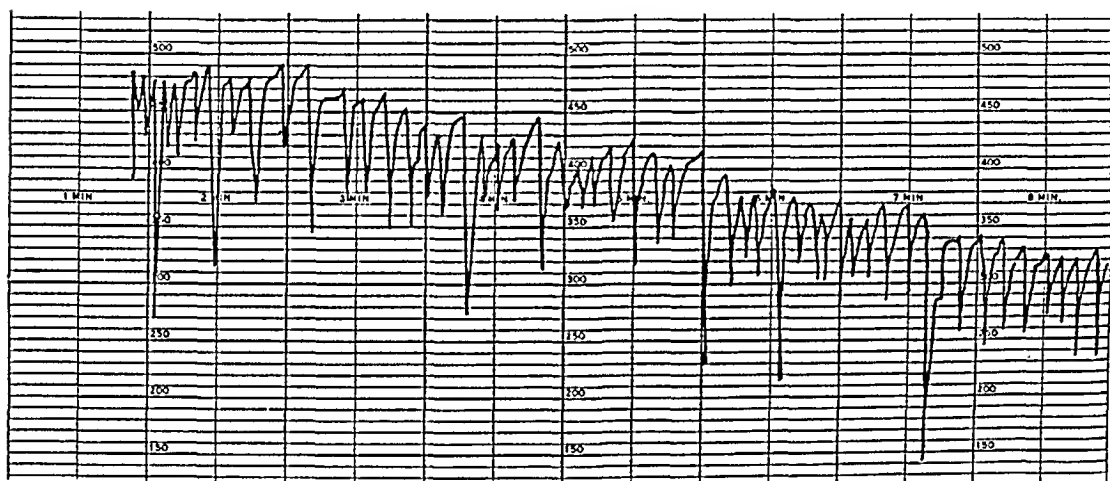


FIG. 2. Irregular sighing respiration in a climacteric patient.

The sighing disappears promptly after the administration of follicular hormone. If the treatment is discontinued it reappears occasionally until adequate treatment is again initiated.

Two thousand successive basal metabolism tracings were investigated regarding the described disturbance of respiration. It was found in 68 cases of which only two were males. Thirty-five of the females were older than 35 years and had symptoms and signs suggesting a disturbance of ovarian function. All but three of the other patients were registered under the diagnosis of hyper- or hypothyroidism, menstrual disturbance, endocrine imbalance, hypo-ovarism, fibroids, etc. In one of the two men with sighing respiration bilateral undescended testes were found.

In the past, when a patient complained very excitedly of pain, dyspnea and palpitation, when flashes of heat existed, and the woman had just arrived at or was in the menopausal age, and, moreover, the clinical examination revealed normal findings, the diagnosis "climacteric neurosis" or neuro-circulatory asthenia was comprehensible.

Sometimes, however, in these patients a series of abnormal signs is found. Occasionally the heart is very excitable, decided pulsations are palpable over the entire precordium, the heart rate is increased, and a systolic murmur may be heard over the apex or the aorta. Tremor, dermatography, sparkling eyes and other signs of hyperthyroidism are present. Sometimes a hypertension exists and values of 200 mm. Hg systolic and 100 diastolic may be observed for several years. When these signs, variously combined, were found, when the symptoms mentioned caused great distress and the electrocardiographic report suggested "evidence of myocardial lesion," then the diagnosis of angina pectoris, myocarditis, or coronary sclerosis was common. These patients were induced to lead a restricted life and were treated for years as cardiac patients with a doubtful prognosis until all symptoms and signs subsided.

### THE ELECTROCARDIOGRAPHIC FINDINGS

In some cases with definite climacteric disturbances it was striking that, during the time of the most pronounced symptomatology, marked alterations appeared in the electrocardiogram although they promptly disappeared on treatment with follicular hormone. Further investigations revealed that patients with ovarian hypofunction, without relation to the climacterium, may present the same electrocardiographic findings.

Frequently, but not always, a sinus tachycardia of 90-120 is found. The auriculoventricular conduction time is occasionally prolonged. The initial complex is not altered. Definite changes are found in the S-T segment and the T-wave.

The most typical finding is a depression of the S-T segment beneath the isoelectric line. This depression may be barely visible or very pronounced. It is usually present in every lead and, therefore, it is most marked in Lead II. Frequently it is accompanied by an alteration of the T-wave. The T-wave becomes lower and may disappear completely. Only rarely is it inverted. The changes of the T-wave are most pronounced in Leads I or III.

It is self-understood that only those changes of the S-T segment which are definitely abnormal have diagnostic value. Slight depression of the S-T segment occurs occasionally in the normal individual after exercise or during a sinus tachycardia. It is also important to rule out preceding treatment with digitalis, since these tracings may be similar in some respects to those of patients who were previously digitalized. It may be emphasized, however, that the slow descent of the S-T segment combined with the steep rise to the T-wave, so characteristic of the digitalis tracing,<sup>31</sup> is usually absent from these tracings.

*Case 1.* This 46 year old patient had suffered from substernal pain for several weeks. During the last week she frequently felt dull pain of variable intensity behind the sternum. The patient also complained of dyspnea and palpitation, independent of

effort. Swelling of the ankles was occasionally noted. Three years previously a panhysterectomy had been performed. The blood pressure was 135/65 mm. Hg. The examination of the heart revealed normal physical findings, except for slight hyperexcitability. There was also a slight tremor; the basal metabolic rate was plus 35 per cent.

The electrocardiogram (figure 3a) shows a sinus tachycardia with a rate of 115. The S-T segment in Lead II is slightly depressed, and there is no T-wave. The patient had never received digitalis. Two thousand units of follicular hormone were injected daily. No other medication save a sedative was given. The electrocardiogram, recorded one week later (figure 3b), shows a rate of 95; the depression of the S-T, most pronounced in Lead II has disappeared, the T in II is normal and positive, and in Lead III the T-wave is less negative than before the treatment. The pain and other symptoms had disappeared in the interim. The blood pressure fell to 112/75 mm. Hg. The basal metabolism was only 11 per cent plus.

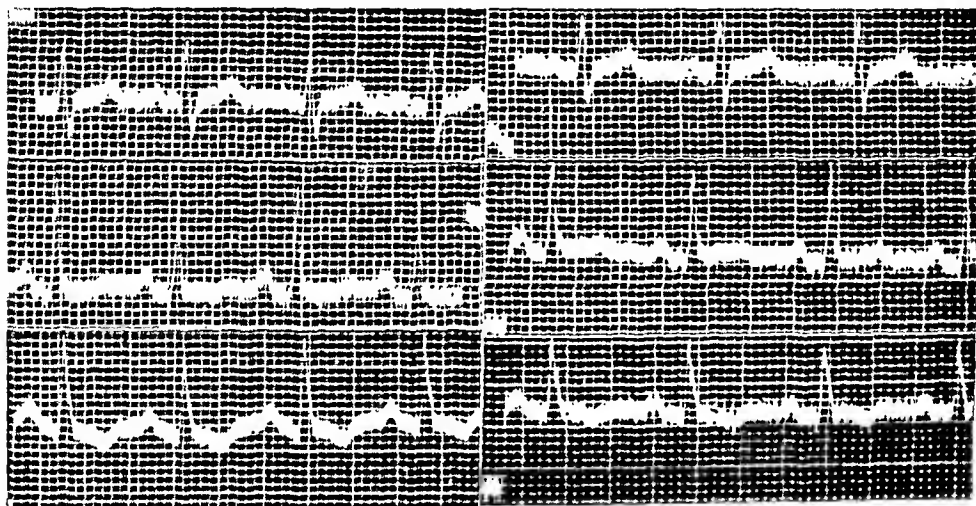


FIG. 3. Electrocardiogram before and after estrogen treatment in a climacteric patient.

*Case 2.* This patient was 59 years of age and complained of "flushes," pain in the precordium, palpitation and dyspnea. A year previously a panhysterectomy had been performed and the symptoms developed slowly one month ago. The clinical examination revealed a hyperexcitable heart with normal physical findings.

Figure 4a shows a regular sinus rhythm with a conduction time of 0.22 second. The initial complexes are normal. The S-T segment in Leads I and II are definitely depressed, the T-waves are almost invisible in all limb leads. In the right arm—precordium chest lead the T-wave is inverted, in the right arm—apex chest lead there is a bifid T. The patient was treated with six intramuscular injections, each containing 10,000 units of follicular hormone. The injections were given twice weekly. No other therapy was employed.

Figure 4b shows the electrocardiogram after three weeks' treatment. The conduction time is normal (0.18 second); the S-T segment and T-waves are also normal in the limb leads as well as in the chest leads. The patient noticed a marked improvement and became symptom free.

*Case 3.* Figure 5 shows very typical and advanced changes. The patient was 48 years old and she had not menstruated for four months. She complained of pains in the region of the heart, hot flashes, palpitation and marked excitability. The blood pressure varied continuously between 180/60 and 220/75 mm. Hg. The heart was

very active, with strong precordial pulsations; however, it was not enlarged. Basal metabolism was  $+70$  per cent.

The electrocardiogram (figure 5) shows a sinus tachycardia with 130 beats per minute and a deep depression of the S-T segment, especially in Lead II. The patient had never received digitalis. Treatment with follicular hormone (10,000 units intra-

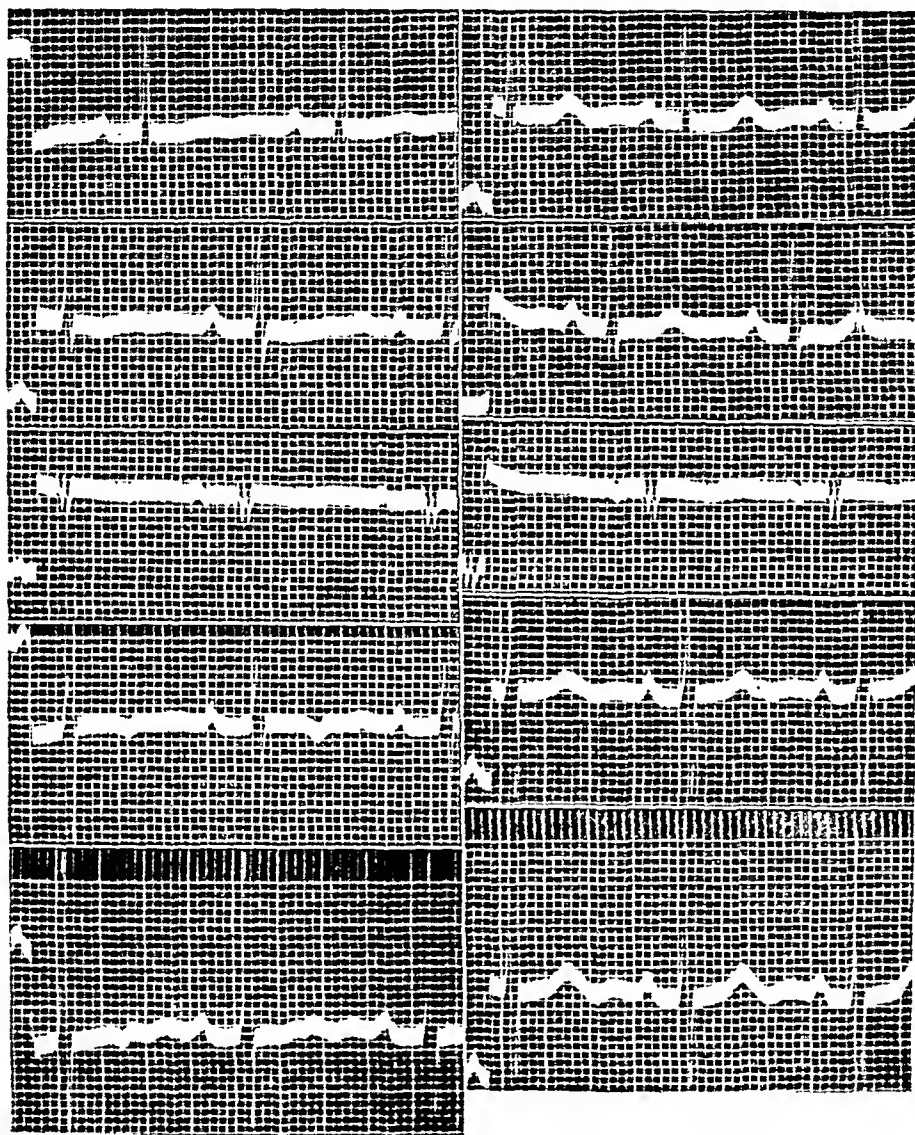


FIG. 4. Prolonged conduction time and abnormal T-waves in a climacteric patient, a normal electrocardiogram appearing after 3 weeks' treatment.

muscularly, twice a week) was instituted; this abolished all symptoms within five weeks.

*Case 4.* This 52 year old patient suffered from palpitation, pain in the precordium while at rest, and a feeling of anxiety. Menstruation was still undisturbed. The blood pressure varied on different occasions between 180/80 and 200/120 mm. Hg, within short intervals of time. The heart was normal in size and form, but hyperexcitable.

The electrocardiogram again shows typical changes (figure 6a). There is again a sinus tachycardia with a rate of 97. The initial complex shows a left axis deviation without widening or splitting. The S-T segment is again markedly depressed. The T-wave is low, especially in Lead II. Within 14 days following the treatment with four intramuscular injections, each containing 50,000 units of follicular hormone, the electrocardiogram was practically normal (figure 6b).

No strict parallelism exists between the extent of alterations in the electrocardiogram and the complaints. One may see patients with marked flushing and palpitation but a normal electrocardiogram; on the other hand, if the electrocardiogram displays the abnormalities mentioned above these symptoms are never absent. In patients who complain of pain in the cardiac region the electrocardiogram is usually altered.



FIG. 5. Marked changes of the S-T segment in a climacteric patient with hypertension, and the changes after treatment. In the tracing on the right the order of leads is I, III, II.

The alterations in the electrocardiogram may be recorded not only in patients in the natural or artificial climacterium (after irradiation or operation), but they may be also seen in young females with ovarian hypofunction.<sup>24</sup> In these patients hypogenitalism usually exists. The menstruation is painful and of short duration, and the menses may disappear for several months. Acrocyanosis, with cold, blue, perspiring fingers, is a frequent finding.<sup>25</sup> The heart may show hyperactivity, but is never enlarged. Tachycardia and a systolic murmur are frequent, and occasionally an elevation of temperature is found, especially before menstruation. If a depressed S-T segment and inverted T-waves, i.e., signs of myocardial damage, are discovered in the electrocardiogram of these cases, the mistaken diagnosis of a myocarditis, sometimes even endocarditis, is commonly made. Some of these patients have been confined to bed for months.

The changes in the electrocardiogram are independent of the signs of hyperthyroidism. This deserves emphasis because in some places hyperthyroidism very

frequently accompanies the menopause.<sup>17</sup> In other regions this combination is much rarer and patients with signs of hypothyroidism are more frequently encountered. Occasionally, mixed forms with signs of hyper- and hypofunction of the thyroid are seen. The changes in the electrocardiogram described above may appear in both types of patients. Naturally they are more frequent in patients with hyperthyroidism, but they disappear after adequate treatment with follicular hormone within a short time whereas the signs of hyperthyroidism still persist. The hyperthyroidism is only a coincidental symptom of the menopausal syndrome. On the other hand, these electrocardiographic changes are not observed in patients with pure hyperthyroidism. The latter group has normal electrocardiograms, sometimes with T-waves of unusual height. Occasionally abnormal S-T segments and T-waves are found, but only in very toxic cases.

The alterations of the electrocardiogram are also not the result of the hypertension. One frequently finds the same changes in patients with a normal blood pressure, especially in younger individuals. In patients with hypertension, too, the

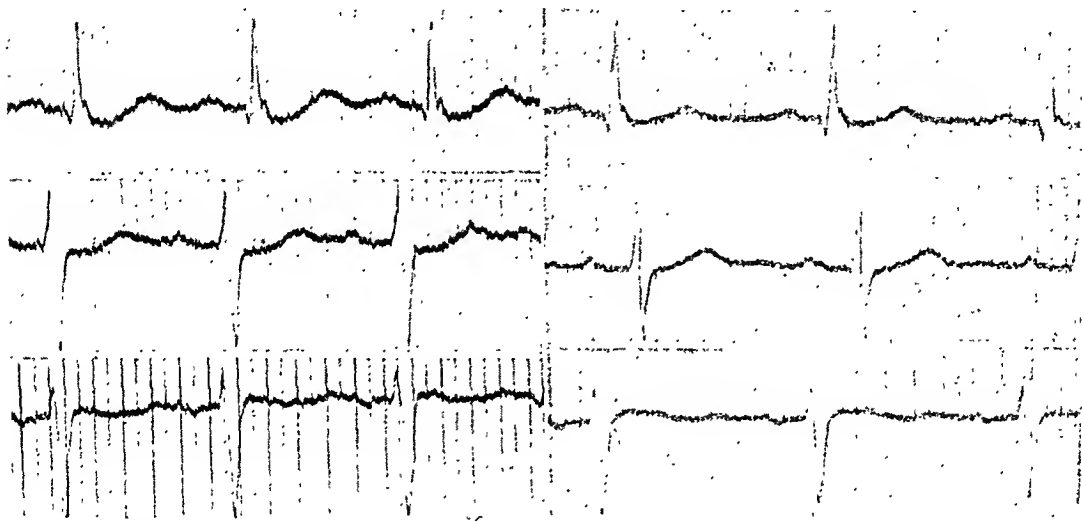


FIG. 6. Electrocardiogram before and after the administration of estrogenic hormone.

electrocardiogram may become normal after treatment with follicular hormone before the blood pressure falls. The electrocardiographic changes may also disappear in climacteric patients with an essential hypertension after the administration of follicular hormone although the blood pressure remains at the same level. Moreover, the changes in the electrocardiogram produced by a hypertension are quite different from those described in this paper, since in hypertension one commonly finds a levocardio-gram which, in the later stages, shows a depressed S-T and T in Lead I and an elevated S-T and T in Lead III. But in the group we are describing, a co-existing hypertension may aggravate the alterations.

The relation between the electrocardiographic changes and the ovarian dysfunction is proved by the fact that the alterations of the final deflection and of the conduction time disappear after a short treatment with follicular hormone.

After interruption of treatment the alterations of the electrocardiogram may reappear after weeks or months. If follicular hormone therapy is again instituted the electrocardiogram becomes normal.

The changes described were observed in 38 cases. Some were treated under the diagnosis of angina pectoris, myocarditis or coronary sclerosis for many months;



the electrocardiogram remained unchanged. Administration of follicular hormone abolished every alteration in one to three weeks.

Since objective signs permitting the diagnosis of an ovarian dysfunction are not available, it is impossible to determine the percentage of these patients in which these electrocardiographic changes appear. They are found only in a minority of the climacteric patients and are by no means a fixed characteristic of this event. As in climacteric hypertension and other climacteric phenomena, a certain "status of the endocrine glands" is necessary for their appearance.

#### HYPERTENSION AND OTHER CIRCULATORY DISTURBANCES IN PATIENTS WITH OVARIAN DYSFUNCTION

Until recently the existence of a climacteric hypertension was denied by very competent observers.<sup>7, 18</sup> Others assume that about 40 to 50 per cent of climacteric females show an elevated blood pressure,<sup>17</sup> and some believe that high blood pressure in the climacterium is a physiological phenomenon. The literature on these questions is extremely contradictory and reflects marked differences of opinion. Since many studies were reported by excellent clinicians, one must assume that the number of cases showing hypertension in the natural or artificial climacterium varies in different countries. Personal experience confirms this assumption, since a change of sphere of activity permitted the writer to observe a difference in the frequency of hypertension in patients with the described syndrome.

If hyperthyroidism is not very marked, the systolic and diastolic blood pressures are increased. Values over 200 systolic and over 100 diastolic are not unusual. In patients with a hypertension of other genesis the blood pressure values may rise to still higher levels in the climacterium. The rapid and frequent fluctuation of the blood pressure is very characteristic. Patients with very outspoken symptoms and signs and with normal blood pressures are especially common among younger females. Here the extirpation of both ovaries and the uterus occasionally does not create any symptom<sup>33</sup> and the blood pressure frequently remains normal.

In the group of patients whose blood pressure increases, a marked dilatation of the heart may be found at times. At times an attack of cardiac asthma or pulmonary edema may appear even before the heart undergoes much enlargement.

*Case 5.* This 45 year old patient, the mother of two children, had always been well. Menopause occurred two years previously. A few months later hot flashes appeared. The physical examination was negative. In the following month the blood pressure gradually increased to 160/80 and 200/95 mm. Hg. Extrasystoles frequently occurred, and signs of hyperthyroidism appeared. The electrocardiogram showed the characteristic depression of the S-T segment, mainly in Lead II. On two occasions, once after a heavy meal and once after great excitement, attacks of pulmonary edema appeared, and injection of morphine and digitalization were necessary. Treatment with follicular hormone quickly abolished all symptoms and signs. Subsequently the blood pressure never exceeded 145/70 mm. Hg, although the signs of slight hyperthyroidism remained. The attacks of pulmonary edema did not recur in the next two years, despite the fact that the patient did not receive any treatment except follicular hormone. The electrocardiogram was normal thereafter.

Two other patients had had attacks of paroxysmal fibrillation in the climacterium only during the period of flushes, palpitation and heart pain.

*Case 6.* This patient, at present 62 years of age, had always been healthy; her menopause occurred 14 years ago. Six years later flushes, palpitation and hyper-excitability appeared. The blood pressure reached 200/110, but fluctuated markedly. For two years, at the height of these symptoms and signs, seven attacks of auricular fibrillation occurred, lasting one to four and one-half hours. Treatment with sedatives and ovarian hormone abolished all the complaints. The heart has remained normal and no further attacks of fibrillation have appeared.

In cases of this kind it will frequently be difficult, or even impossible, to rule out another cardiac lesion, for example coronary sclerosis; however, the possibility of a disturbance connected with the climacterium should always be considered and adequate treatment should be instituted.

#### TREATMENT WITH ESTROGENIC HORMONE AND THE ELECTROCARDIOGRAM

In every case the administration of follicular hormone was followed by a very rapid relief of symptoms and a return of the electrocardiogram to normal, if sufficient doses were administered. The tachycardia which was frequently present disappeared, the depression of the S-T segment and the abnormality of the T-waves changed gradually to terminal deflections of normal appearance. In some cases the electrocardiographic changes have vanished within eight days after the administration of as little as 1000–2000 international units daily. In other cases injections of 10,000 or 50,000 units two to three times weekly for three to four weeks were necessary to produce an improvement. The doses necessary naturally differed in each case. In some younger patients the injection of gonadotropic hormone seemed preferable. At the beginning, suppositories or injections were usually given, depending on the severity of the case, but later on, after the effect was established, oral administration was usually sufficient. In the females who were still menstruating the best results were obtained when the follicular hormone was given during the first 10 to 15 days after menstruation. After the menopause the patients were always informed that bleeding might again occur during the treatment.

The treatment in younger patients and in patients with disturbances of the menstruation was never undertaken without consultation with a gynecologist. If fibroids were present the follicular hormone was employed very cautiously. When bleeding occurred during treatment, in a patient after the menopause, the patient was also sent to a gynecologist. The value of this procedure was illustrated by one case, a 56 year old patient, who developed slight metrorrhagia after the use of 20 suppositories each containing 5000 units of follicular hormone. The gynecologist found a uterine carcinoma, which was operated upon. There is no reason for presuming that the treatment itself may cause a carcinoma.<sup>14</sup>

## PATIENTS WITH ORGANIC HEART LESIONS AND THE CLIMACTERIC

If the disturbances accompanying the climacterium have such a profound influence on the heart of the healthy female, it is easy to understand their importance for patients who already harbor an organic heart lesion. It has been known for a long time that an organic valvular lesion or a hypertension may be fully compensated, and even asymptomatic, for years and decades until the mid-forties are reached; then quite suddenly and unexpectedly decompensation sets in.<sup>17</sup> The heart dilates quickly, cardiac asthma, pul-

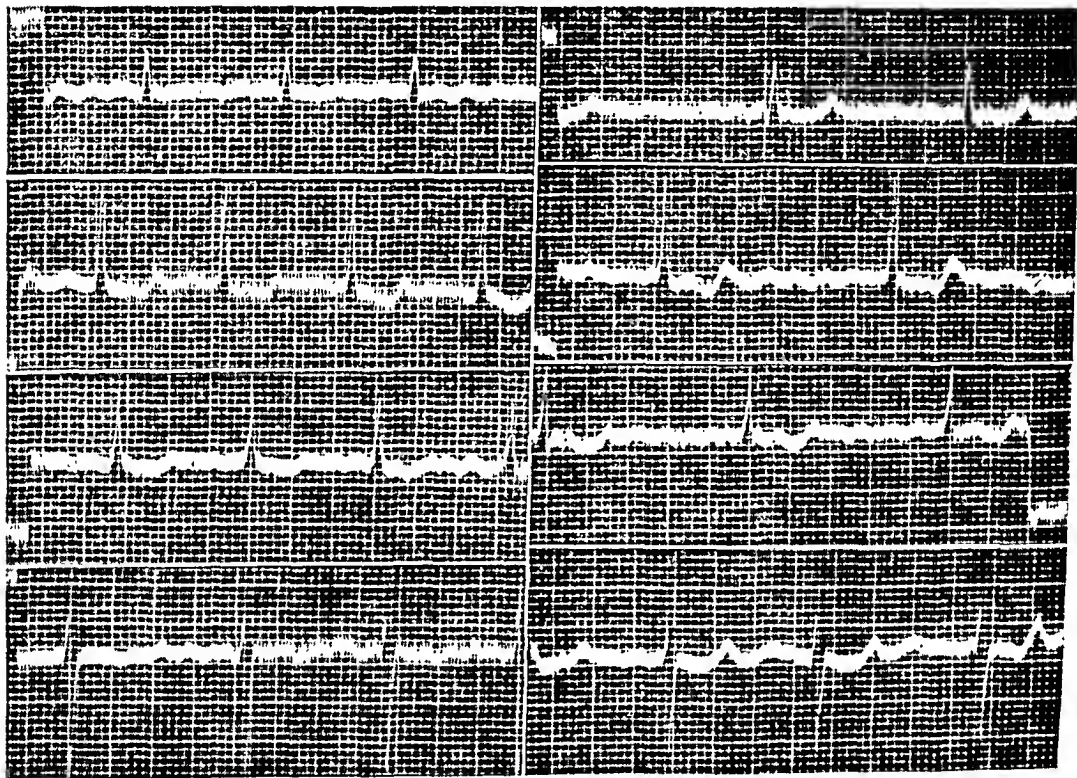


FIG. 7. Case of mitral stenosis and auricular fibrillation in the climacterium before and after treatment.

monary edema and peripheral congestion appear. This event is not rare and can be avoided. The estrogenic function of every cardiac patient should be continuously controlled, especially if the patient is in the age period during which climacteric disturbances occur. Prophylactic treatment with follicular hormone, if instituted early, might save many lives.

*Case 7.* Figure 7 was transcribed from a patient with mitral stenosis of 40 years' duration. The patient had polyarthritis at the age of eight. Five years previously the uterus was extirpated because of fibroids. Shortly afterward she began to complain of breathlessness and palpitation. During the last year the patient suffered from pain of a "crushing" and non-radiating character; this was felt behind the sternum and recurred three to four times an hour both day and night.

On admission mitral stenosis without congestive failure was found. The basal metabolism was  $-10$  per cent, and the blood pressure was 110/80 mm. Hg. The electrocardiogram revealed auricular fibrillation (figure 7a) with a depressed S-T segment in Leads II and III. The T-waves are almost invisible in all leads. No axis deviation was present. The patient was treated with  $1\frac{1}{2}$  gr. of digitalis, twice daily. Three weeks later the electrocardiogram shows (figure 7b) a slower heart rate; the depression of the S-T segment is still present (digitalis?), but the T-waves are much higher, especially in Leads I, II and the chest lead (left leg to the apex).

*Case 8.* A 40 year old patient, with an insufficiency of the aortic valve and a mitral stenosis, complained of palpitation, oppression, dizziness and dyspnea only on exertion. Her menstruation was irregular and lasted only one day. The physical findings were those of a rheumatic mitral and aortic lesion without congestive heart failure. The electrocardiogram (figure 8a) showed a sinus tachycardia with a conduction time of 0.21 second. The S-T segment is depressed in all leads, but mostly in Lead II. There are no T-waves.

After the daily administration, for 20 days, of suppositories containing 5000 units follicular hormone, the heart rate is slower, the P-R distance is shortened to 0.18 second (figure 8b), the S-T segment and T-wave are normal.

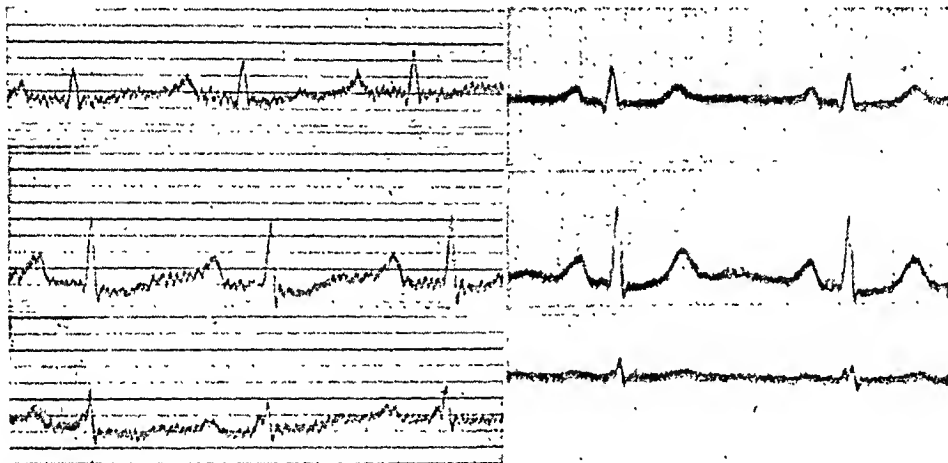


FIG. 8. Case of aortic and mitral lesion before and after treatment; note the prolonged P-R interval and the abnormal T-waves before treatment.

In patients with an essential hypertension the timely administration of follicular hormone may cause an astonishing improvement of the symptoms even without a change of the blood pressure.<sup>24</sup>

### MYOMA HEART

In this connection passing allusion may be made to the question of the existence of a so-called "myoma heart." For more than 50 years cardiac changes have been described in patients with uterine fibroids.<sup>2, 3, 19, 28</sup> The relevant literature is enormous. Time and again changes in the hearts of patients with uterine myomata have been denied. The circulatory disturbances are ascribed frequently to the mechanical effect of a large tumor, to the accompanying anemia, or to the formation of an unknown substance by

the tumor. These arguments were disputed by others who found evidences of cardiac damage without anemia, without a large tumor, etc. Considerable confusion has been caused by premature conclusions from a small number of cases or even from a single case. The fact that the anatomical examination of the heart did not reveal any abnormal findings<sup>16</sup> does not prove very much, since the histological method is completely inadequate for demonstrating many other types of myocardial damage. A heart damaged by toxins or a heart weakened by chemical poisons frequently fails to exhibit any changes in the myocardium which can be histologically diagnosed. In recent years, however, most pathologists, gynecologists, and cardiologists deny the existence of a "myoma heart," although the possibility of toxic or hormonal effect from the fibroids upon the heart is mentioned. Ovarian dysfunction has been both assumed<sup>28</sup> and denied.<sup>8</sup>

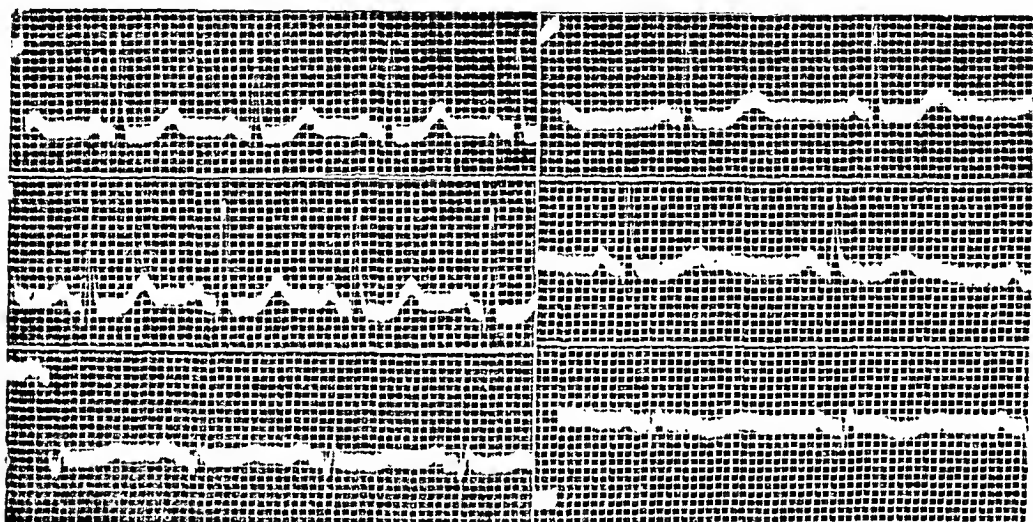


FIG. 9. Electrocardiogram of two cases of fibroids.

In patients with uterine fibroids we observed electrocardiograms which are very similar to those found in females with hypo-ovarium. Here also the depression of the S-T segment below the isoelectric line, especially in Lead II, is the most constant finding. Figure 9 shows electrocardiograms of two patients with uterine fibroids (43 and 57 years of age) in which the depression of the S-T segment is clearly visible. In more advanced cases alterations of the T-waves also appear.

Fetter and Schnabel described abnormal electrocardiograms in patients with fibroids. They ascribed the changes in their cases to the abnormal position of the diaphragm, caused by the large tumors. A study of their paper reveals, however, that the observed alterations in the electrocardiogram are very similar to those described in this paper as a consequence of a dysfunction of the ovaries.

Further studies now in progress should answer the question as to whether the heart damage, which in our opinion occurs undoubtedly in patients with fibroids even without anemia and with small tumors, may be ascribed to the same mechanism.

Most fibroids cause symptoms in the climacterium and in the preclimacteric age. Moreover, an interrelation between uterus and ovaries seems to be established, among other things, by the fact that extirpation of the uterus without any damage to the ovaries or their blood supply may cause "climacteric" symptoms. Accordingly there seemed to be some basis for the opinion that in these cases we are dealing with the same disturbance.

We may assume that in a myoma heart the disturbance is caused in a way which is very similar to that discussed in this study. The electrocardiographic changes, which Fetter and Schnabel explained by a mechanical displacement of the heart by the tumor, actually are quite different from those which may be found with abnormal elevation of the diaphragm.

### DISCUSSION

For several years the symptoms and signs of the climacterium have been attributed to an ovarian dysfunction. They are not ascribed to the menopause itself, despite the fact that frequently they coincide in time. The term, "circulatory disturbances of the menopause," though in vogue, causes errors and misunderstanding. We found the same disturbances in young females with hypo (dys-?) function of the ovaries. They may be observed years before the menopause and even 10 to 15 years following it.

In analyzing the underlying disturbances, discussion may be confined to the alterations of the electrocardiogram, since they are easily and objectively controlled. These electrocardiographic changes could be evoked by a lesion of the heart muscle itself or by an involvement of the coronary vessels and a secondary change in the condition of the myocardium.

As yet no proof of a primary tissue lesion has been obtained in these patients. In this connection the interesting changes in the content of serum calcium in conditions of hyper- or hypofunction of the female sex glands may be mentioned.<sup>22, 35</sup> The electrocardiograms described, however, do not show the changes of the R-T interval which are typical for hypocalcemia.

A number of observations and facts speak in favor of the responsibility of the narrowing of the smaller coronary arteries; this, in turn, may be caused by an involvement of the vascular wall or by an abnormal reaction of the vessels to substances or hormones in the circulating blood; abnormal quantities of these hormones might also be present.

(1) Rapid changes of the electrocardiogram are not infrequently observed. The form of the T-waves or of the S-T segment may undergo alterations within a few hours. Observations of this kind are not easily explained by a structural myocardial lesion. Moreover, these rapid changes are common in disturbances of the blood supply to the heart caused by syphilitic or sclerotic involvement of the coronary arteries. (2) Other vascular phenomena are frequently observed in such patients. For many years the picture of acrocyanosis in patients with hypogenitalism and dysfunction of the ovaries has been a familiar one; this is also successfully treated with follicular hormone. It is also known that numbness of the extremities, for-

mication, sensations of heat, local congestion, cold hands and feet, paresthesia of the arms and legs, and finally the changes in the systolic and diastolic blood pressure, are vascular phenomena which are amenable to hormonal treatment. (3) Anginal pain with typical radiation may appear. (4) Retinal vascular changes in climacteric females with hypertension have been observed; they disappeared after the administration of follicular hormone.<sup>6, 6a</sup> (5) Vasodilators (nitroglycerin, theobromine, papaverine) have an excellent effect in patients of this kind. This has been known for many years and was discovered purely empirically. (6) Many investigators have found that female sex hormone has a vasodilating effect. Its therapeutic use in the treatment of organic peripheral vascular diseases has been frequently recommended.<sup>21, 26, 27</sup>

Nevertheless, no proof has been obtained up to the present time for the validity of the above explanation although it seems to possess more probability than the presence of a primary tissue lesion.

The finer mechanism and primary cause of the disturbance may be explained by the imbalance of the endocrine glands resulting from the interruption of the normal function of the ovaries. The inhibitory action of the follicular hormone on the hypophysis ceases, and therefore an increased formation or unopposed action of various hypophyseal hormones results. The increased formation of the thyrotropic and adrenotropic hormones has been proved. Some observers also assume that a hypersecretion of vasopressin occurs.<sup>25, 34</sup> It is possible that these hormones cause hyperexcitability and hypercontractility of the heart and an increase of the blood pressure; this augments the work of the heart muscle and increases its need for oxygen. This action, in conjunction with even a slight narrowing of the vessels, may cause a relatively inadequate blood supply to the hyperactive heart, may cause pain, and the alterations in the electrocardiogram described.

Whatever the finer mechanism of the damage to the heart may be, it is clear that it is not a failure to form follicular hormone but the abnormal action of the other glands which is responsible for the signs and symptoms. Vasomotor disturbances, such as flushes, are frequently observed at a time when satisfactory ovarian function is still present.<sup>1, 14, 29</sup> Observations of this nature and the fact that "climacteric disturbances" may appear after hysterectomy without injury to the ovaries represent the basis of the postulation that an unknown hormone is formed in the uterus.<sup>14</sup>

There is considerable evidence to support the assumption that the disturbances described above are not confined only to the heart muscle and the circulatory system. Not rarely, by careful investigation and examination, abnormal conditions are found in other organs. Most of them were already known before the changes in the heart were appreciated. The climacteric arthralgia<sup>10</sup> and mental disturbances have already been mentioned. Albuminuria is not rarely observed,<sup>4</sup> and frequently pitting edema appears on the upper or lower extremities and occasionally even on the face. These phenomena, in conjunction with the symptoms and signs described, are frequently the occasion for unnecessary digitalis therapy, since congestive heart failure is mistakenly diagnosed. The deep sighing respiration provocative of a feeling of

oppression and breathlessness, which disappears like all other related phenomena after the administration of follicular hormone, points to the existence of an abnormal situation in the respiratory centers. Changes in gastric acidity,<sup>9</sup> obstipation or diarrhea have been observed. It seems permissible to assume that many, if not all, tissues occasionally may be involved. Unfortunately for most of them no method of examination as sensitive and as exact as the electrocardiogram for the heart is available.

This deep sighing has been described by P. D. White as a symptom of neuro-circulatory asthenia.

A great deal has also been written about the male climacteric. Recently its existence has been denied on the basis of theoretical arguments. It is true that symptoms and signs as pronounced as in climacteric females are never observed in males, but one occasionally meets patients with oppression or pain and pressure in the heart region without any sexual disturbance and without any evidence of an organic cardiac lesion for many years, and usually a diagnosis of cardiac neurosis is made. In these patients one may occasionally find a slight, but definitely abnormal depression of the S-T segment. Proof that the same or a similar disturbance, but one of lesser severity, exists here, could not be obtained, because no opportunity has as yet been afforded in these patients to use hormonal treatment with substances of the same activity as those available for treatment of the female climacteric.

### SUMMARY

In patients with hypofunction (dysfunction) of the ovaries prolonged conduction time and abnormal sinistral deflections may be found in the electrocardiogram. The alteration of the sinistral deflection is usually most pronounced in Lead II.

These findings disappear after the administration of follicular hormone.

A disturbance of the respiration, characteristic of these patients, is described.

Similar changes may be found in patients with uterine fibroids.

The finer mechanism of the described lesions and their clinical importance are discussed.

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## TRICHINIASIS: CLINICAL CONSIDERATIONS \*

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TRICHINIASIS is an acute febrile illness caused by a nematode, *Trichinella spiralis* ["little spiral hair"]. This disease is the only metazoan infestation in humans which is regularly accompanied by fever. It is a much more common disease than is generally recognized, having been found in from 10 to 25 per cent of autopsies in which trichinae were specifically searched for.<sup>1, 2, 3, 4, 5</sup> As summarized by Hall<sup>6</sup>: "Nine groups of workers from 24 hospitals in 11 widely scattered cities in the United States found over 12 per cent of cadavers with evidence of trichinous infection. Trichinosis is a major public health problem." Scheifley<sup>7</sup> feels that the evidence indicates an incidence among adults in the United States of about 20 per cent. It is clear that Magath<sup>8</sup> was not exaggerating when he said that "in the United States 10 to 20 per cent of adults have acquired trichinosis, although most of them have never had symptoms suggestive of trichinosis." Hall and Collins<sup>9</sup> clearly state the gravity of the situation with the conservative estimate that "there are probably several million persons in the United States who are infested with trichinae, among whom are possibly several hundred thousands who have had clinical trichinosis never diagnosed as such, and there are possibly several thousand deaths annually from this cause."

Season and sex have no appreciable influence on the incidence of the disease. Age plays a rôle only because children under 3 or 4 rarely eat foods containing trichinae. All ages are susceptible, however, and in animal experimentation it is easier to infect the young than adults. An attack of trichiniasis apparently does not confer a permanent immunity, as patients are occasionally seen who have had two attacks (such as case 5 in this paper). The frequency of a recognized second or third infestation would undoubtedly be greater if the clinical diagnosis were made more often and if patients always knew or remembered that they had had trichiniasis years before.

Man is infected by eating meat harboring trichinae. When flesh containing the larvae is ingested, the capsules of the cysts are dissolved by the digestive juices and the larvae penetrate into the intestinal mucosa. Here the male and the female sexual forms develop and copulate about 40 hours after the meat is eaten. The pregnant females, still residing in the intestinal mucosa, lay their eggs—about 1,000 embryos by each female. The newly born trichinae enter the intestinal lymphatics about the fifth day, and are disseminated throughout the body via the blood stream. The predominant localization of the larvae is in the voluntary muscles, where they

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are first found about the sixth to eighth day after ingestion and where they eventually become encapsulated in an ovoid capsule, at first translucent but later infiltrated with lime salts.

The first complete description of the *Trichinella spiralis* was published in 1835 by Owen, after Hilton had discovered the capsule and Paget the enclosed worm. Twenty-five years later the scene shifts from London to Dresden, where Zenker demonstrated the danger of this parasite by finding it at autopsy in the muscles of a patient supposed to have died of typhoid fever. He discovered that the patient had eaten meat from a certain pig and that many others who had partaken of the same meat were ill. The final link in this brilliant clinicopathological demonstration was the finding of trichinae in the muscles of that hog. For a number of years after this, most of the work on the disease was done in Germany, where there were many cases and some very large outbreaks. During the past 25 years almost all the advances—clinical, experimental, and immunological—have been made in the United States. The history of the early work on the parasite, its development in the infested organism, and the pathological changes in the muscles are so admirably described by Sobel<sup>10</sup> that no further mention of these aspects will be made in this paper.

The trichina has been found in many species and can be experimentally transmitted to a great many others. The most common natural hosts are the rat and the pig, which serve as a large reservoir keeping the species from becoming extinct. Man is infected in almost all cases by eating pork products, such as undercooked ham and pork, salami, liverwurst, bratwurst, pig's feet, smoked and pickled ham and pork, sausages ("hot dogs"), summer sausage (cervelat), and hamburgers, which frequently contain ground pork scraps. There has been an outbreak in this country from bear meat<sup>11</sup> and one in Germany from polar bear meat.<sup>12</sup> In some countries the disease is probably transmitted to humans by improperly cooked dog meat.<sup>13</sup>

Prevention of trichiniasis is relatively easy compared to that of many other diseases of man, since the only measure necessary in the vast majority of cases is the thorough cooking of all pork and products containing pork. This, incidentally, will also prevent infestation with *Taenia solium*, the pork tapeworm. The trichinae, with a thermal death point of 55° C., are not particularly resistant to heat. The Bureau of Animal Industry recognizes 137° F. (58.3° C.) as the minimum temperature to which pork—including the interior of the piece of meat—should be cooked. Cameron<sup>14</sup> warns that "all pork should be cooked until the natural colour is gone." One might hesitate to eat pork at all after reading Dickman's recent findings<sup>15</sup> to the effect that 10 per cent of all pork sausage obtained at random in the markets of a large city contained trichinae. But Hall and Collins<sup>9</sup> have pointed out the value of pork from the economic and dietary angles, and have suggested methods of preparing pork products for safe consumption. A fact not generally known is that the federal meat inspection regulations no longer

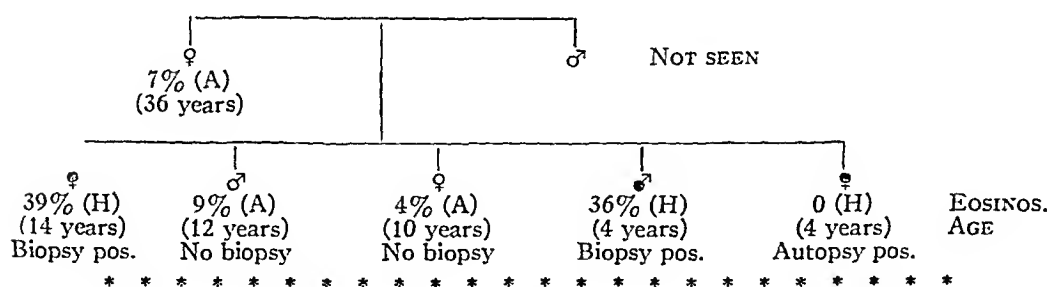
require a microscopic examination for trichinae. As Pepper<sup>16</sup> has pointed out: "Inspection of pork [for trichinae] has proved too difficult and expensive to be carried out routinely with success. Also many families grow and butcher their own animals. Microscopic examination is necessary for satisfactory inspection and this has proved impracticable." The Bureau of Animal Industry has issued the following warning: "Dry-salt pork, pickled pork, and smoked pork previously salted or pickled, provided the curing is thorough, are practically safe so far as trichinosis is concerned, but as the thoroughness of the curing is not always certain, such meat should also be cooked before it is eaten."

If trichina infestation of pigs could be diminished, the incidence of human infestation would be correspondingly lessened. The rat has been considered responsible for much porcine trichiniasis; but most recent writers<sup>5, 14</sup> feel that this is not the crux of the problem. As Wright<sup>5</sup> has recently stated: "It is my opinion that the rôle of the rat as a source of swine trichinosis has been largely over-emphasized. The hog fed on uncooked garbage is today the major source of human trichinosis." Most authorities now agree that thorough cooking of all garbage fed to swine would materially reduce the incidence of human trichiniasis.

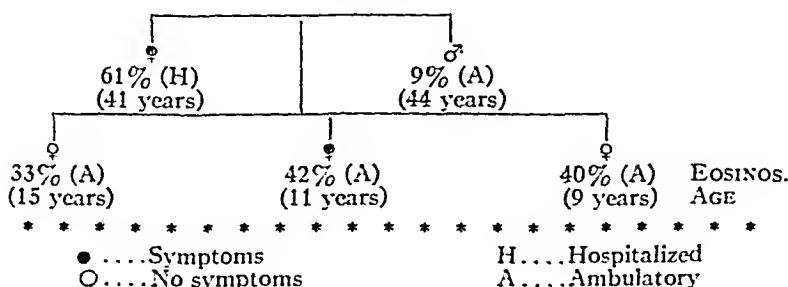
There have been many epidemics in which large numbers of individuals have been infected from the same meat supply. In the latter part of the

As an illustration of the widespread occurrence of mild or unrecognized cases of trichiniasis in the members of the family of patients with this disease, the charts of two families whom we studied with blood smears are shown here.

## FAMILY D.



## FAMILY M.



last century there were two large outbreaks in Germany, one involving 337 persons and the other 250. Two outbreaks of interest, because of the source of infection, were those described by Walker<sup>11</sup> in this country, due to bear meat, and by Weitz<sup>12</sup> in Germany, due to polar bear meat. Barrett and Sears<sup>17</sup> in 1938 recorded an epidemic of 73 cases with 6 deaths in Capac, Michigan with a population of only 800. Drake, Hawkes, and Warren<sup>18</sup> give a very good account of the history of epidemics of this disease. Spink and Augustine,<sup>19</sup> who have done a great deal of excellent work in Boston on trichiniasis, review the general epidemiological knowledge in a most satisfactory manner.

The mortality in various outbreaks has varied from 1 to 30 per cent, averaging about 10 per cent. The figure tends to be higher in the larger outbreaks. In sporadic cases, which are common in this country, the mortality is definitely under 5 per cent. The percentage depends to a great extent on the number of relatively symptom-free infected individuals who are included in the series. Trichiniasis would not seem nearly so scarce if we would be more thorough in investigating the families of persons found to have the disease. The inclusion of those with either very mild symptoms or no symptoms at all, in whom the diagnosis is made by a consideration of the history, physical examination, and laboratory findings, would materially lower the apparent mortality. It must be remembered that "not all persons who eat trichinous flesh have the clinical disease. A limited number of the worms may not cause noticeable symptoms."<sup>20</sup>

#### CLINICAL AND PATHOLOGICAL

Immediately after the ingestion of trichinous meat there may occasionally be symptoms of a mild gastrointestinal upset, with nausea, vomiting, and abdominal pain. Twenty-four to seventy-two hours later the period of invasion begins. Anorexia, nausea and vomiting, diarrhea, and generalized abdominal pain are often present. These symptoms may be severe enough at times to resemble cholera. The incubation period—from the ingestion of the trichinae to the first symptoms—is usually given<sup>17, 18, 21</sup> as 2 to 27 days, with an average of about 7 to 12 days, for cases occurring during an outbreak. In sporadic cases, however, it seems to be much shorter, having been 48 to 72 hours in many of our cases. The period of dissemination begins about 6 to 10 days after eating the meat. As stated previously, the dissemination of the larvae consists of their migration from the intestinal mucosa through the lymph and blood streams.

The larvae were first found in the blood in 1909 by Herrick and Jane-way<sup>22</sup> by diluting a sample of blood with 10 parts of 3 per cent acetic acid, centrifuging, and examining the sediment. This method is still in use, and the larvae have been found in the blood from the sixth to the twenty-second day of symptoms in almost 50 per cent of the cases in which they have been searched for. Van Cott and Lintz<sup>23</sup> were the first to discover the larvae

in the spinal fluid in 1914, since which time many others have found them there.<sup>24, 25, 26, etc.</sup> The adult worms have occasionally been found in the stools, even many weeks after the infection,<sup>27</sup> although this is a relatively rare finding. The larvae have also been found in the pleural and peritoneal exudates, milk of a nursing woman, and pus from a furuncle.<sup>24</sup> They have not been observed in the urine or in the pericardial fluid, to the best of my knowledge. Many tissues and organs may contain the embryos: the brain and meninges<sup>28, 29, 30</sup>; intestinal mucosa; mesenteric lymph nodes, liver, lungs, pancreas, myocardium<sup>30</sup>; placenta, mammary gland, kidney, retina, and bile.<sup>28</sup> Frothingham,<sup>30</sup> who gave an excellent description of the pathology of trichiniasis in 1906, based mostly on the work of Cohnheim, observed that the embryos enter the organs by "breaking out of the [blood] vessels." The site of predilection and the final resting place of most of the larvae is the skeletal musculature, where they "grow for about two weeks, when they begin to coil up and encyst. The cyst wall is distinct by the end of the sixth week and becomes complete in about three months. The capsule begins to calcify in about six months. It is believed that these embryos may live 20 to 30 years in the cyst in the human."<sup>18</sup> Frothingham thought that the capsule is formed of connective tissue, but MacCallum<sup>31</sup> considers that it is formed by the worm, as "the host does not produce such a peculiar capsule for any other foreign body."

#### GENERAL SYMPTOMATOLOGY

Fever is almost always present during the acute stage of the disease. In most cases the temperature varies from 100° to 103° and lasts from a few days to several weeks. In other cases there is high fever, 104° to 106°, which may last many days. This type of fever curve, with the relative bradycardia usually present, produces a chart similar to that seen in typhoid. Chills were present in 8 of 35 cases in the series of Spink and Augustine.<sup>32</sup> Hypotension (systolic under 100) was noted in 12 of their cases. Sweating and itching are fairly common, according to Salzer,<sup>33</sup> although this is not the usual experience. Some symptoms such as fever, sweating, chills, itching, hypotension and weakness, are probably mainly due to toxemia from the presence of the larvae and from muscle destruction. Other symptoms and signs, such as dehydration, acidotic breathing, tetany, and weight loss, are attributable mostly to vomiting and diarrhea, with the consequent upset in the water and salt metabolism. Aside from the results of the toxemia and of the derangement of salt and water metabolism, the clinical picture will depend on the tissues and organs invaded by the larvae.

#### GASTROINTESTINAL TRACT

The presence of the trichinae—adults and embryos—in the intestinal lumen and mucosa is responsible for the gastrointestinal symptoms which are usually present during the period of invasion; i.e., second to eighth days

after eating the infected meat. About 70 per cent of patients have gastrointestinal symptoms of some sort. These consist of anorexia, nausea and vomiting, generalized abdominal discomfort or cramps, occasionally constipation but more often diarrhea, very rarely intestinal hemorrhage. The diarrhea may be so severe that, in conjunction with the fever, prostration and toxemia, cholera or dysentery may be simulated. The diarrhea and vomiting may cause marked dehydration, acidosis, weight loss, exhaustion, and even death.

### MUSCULATURE

The migration of the larvae through the blood stream into the muscles results in a myositis. Clinically the muscles most often affected are the gastrocnemii, deltoids, biceps, and those around the eye; less often the diaphragm, various muscles of the extremities and of the abdominal wall and thorax; rarely but of greater seriousness, the intercostals, the muscles of mastication, deglutition, and speech; and occasionally the cardiac musculature. At autopsy the diaphragm is probably the most frequently involved; and large numbers of larvae are sometimes found in the muscles of the glottis, larynx, and tongue,<sup>34</sup> in addition to the muscles listed above. Invasion of the muscles of the trunk or extremities is manifested by edema, pain and tenderness. The pain, if located in the abdominal wall or back, may be severe enough to simulate a colic: renal, biliary, intestinal, etc. The tenderness may be slight or extremely marked. There may be weakness of the muscle or even paralysis, suggestive of poliomyelitis. In Spink and Augustine's series,<sup>32</sup> 26 of 35 patients complained of muscle pains. The eye muscles are frequently involved, causing pain and burning in the eyes, conjunctivitis, occasionally subconjunctival hemorrhages, photophobia, paresis, diplopia, and edema. Edema of the eyelids is one of the most constantly observed clinical features of trichiniasis. A history of puffy eyelids or actual edema noted on physical examination was present in almost 60 per cent of 12 ambulatory cases and in 80 per cent of 15 hospitalized patients whom I have seen in the past five years. From the viewpoint of the ophthalmologist, who is occasionally the first to see the patient, the "most characteristic ocular sign is chemosis of the bulbar conjunctiva, bilateral as a rule."<sup>35</sup>

Involvement of the muscles of the respiratory tract is usually serious, as life may be threatened by asphyxia due to edema of the pharynx and larynx.<sup>36</sup> Inflammation of the diaphragm and intercostal muscles may lead to painful breathing or respiratory embarrassment; and paralysis of the respiratory muscles may occur.<sup>12</sup> The muscles of mastication are sometimes the seat of edema, occasionally simulating mumps.

### RESPIRATORY SYSTEM

Respiratory signs and symptoms are frequent, having been present in 50 per cent of 102 cases reported by Minot and Rackemann.<sup>37</sup> The pharynx, larynx, trachea, bronchi, lungs and pleura may be affected. Cough, sputum

(usually mucopurulent), dyspnea, cyanosis, signs of pulmonary congestion or consolidation, alone or together, may be present. Bronchopneumonia or lobar pneumonia may be simulated or actually present.<sup>37</sup> Pleurisy and pleural effusion also occur. Hemoptysis occurring during the course of an attack of trichiniasis has been reported<sup>38</sup> in three cases.

### NERVOUS SYSTEM

Symptoms and signs of central nervous system and peripheral nerve involvement are fairly common and may be very severe. Diplopia and paresis or paralysis of the eye muscles are not rare; and it is frequently not realized at first that the lesion is a myositis rather than damage to a cranial nerve or meningeal irritation. Reflex changes are common, the most usual abnormality being a diminution or loss of the knee jerks. These were absent in 10 per cent of the cases seen by Merritt and Rosenbaum.<sup>39</sup> The ankle jerks may also be lost, as well as the biceps reflex and others. Signs of meningeal irritation may be present, such as stiff neck, positive Kernig and Brudzinski signs, headache, blurred vision and diplopia.<sup>40</sup> Meyer<sup>25</sup> reported three cases simulating meningitis with trichina larvae in the spinal fluid. Blumer<sup>26</sup> and Merritt and Rosenbaum<sup>39</sup> have seen cases with hemiplegia and the larvae in the spinal fluid. Willett and Pfau<sup>41</sup> saw one case with a temporary paralysis of a leg; and Barrett and Sears<sup>17</sup> reported two cases with paralysis of the extremities. One of our cases (number 2) showed an absence of knee jerks and biceps reflexes, stiff neck and positive Kernig and Brudzinski signs, carpopedal spasm, paresis of the left side of the face, unequal pupils, and a terminal hyperpyrexia up to 109°. General signs of cerebral involvement, such as coma, severe mental depression and disorientation, may be found.<sup>12</sup> Peripheral neuritis occurs occasionally, although more often there is muscle weakness and pain, which may simulate neuritis or a lesion of the anterior horn cells—poliomyelitis, for example. Involvement of the cranial nerves occurs very rarely. Encephalitis due to the presence of the embryos in the brain has frequently been reported,<sup>28, 29, 30, 42</sup> with a variable and bizarre neurological picture, as a rule. Hassin and Diamond<sup>29</sup> point out that trichiniasis may produce a typical picture of acute non-suppurative meningo-encephalitis with degenerative changes due to toxins and with inflammatory changes due to the presence of the larvae. From what has been said it will be apparent that Merritt and Rosenbaum<sup>39</sup> summarized the situation well when they warned that cases of trichiniasis with neurological manifestations must be differentiated from poliomyelitis, encephalitis, encephalomyelitis, meningitis, polyneuritis, dermatomyositis, and periarteritis nodosa.

### CARDIOVASCULAR SYSTEM

Cardiovascular complications have been stressed clinically only during the past few years, mainly by Spink and Augustine.<sup>32, 43</sup> Symptomatically



there may be dyspnea and orthopnea, cyanosis, palpitation and tachycardia. On examination one may find the signs of congestive heart failure or merely of a myocardial involvement, such as a systolic murmur at the apex, poor quality of the sounds, tachycardia, hypotension, irregularity of rhythm. An acute myocarditis, which has been demonstrated pathologically in humans and in animals, accounts for these signs and symptoms. The myocarditis is caused by the presence of the larvae in the myocardium, producing an inflammatory reaction.<sup>43, 44</sup> Hypotension (systolic under 100) was present in 12 of Spink and Augustine's 35 cases. Other vascular changes include congestion and hemorrhages in the conjunctivae and sclerae, lungs, and gastrointestinal tract. Edema in various parts of the body is probably largely a manifestation of capillary damage. Thrombosis, phlebitis, and embolism, including pulmonary, have been noted.<sup>12, 48</sup> Electrocardiographic changes were found in 6 of 17 patients in whom tracings were taken by Spink and Augustine.<sup>32</sup> The changes consist of: inversion of the T-wave, especially in Lead II; low amplitude of the QRS complex; and occasionally evidence of intraventricular block. Beecher and Amidon<sup>45</sup> saw one case with temporary nodal premature contractions, and another with temporary prolongation of the P-R interval. Death from myocarditis usually occurs from four to eight weeks after the onset of the illness.<sup>43</sup> An interesting observation is the relatively frequent occurrence of encephalitis and myocarditis in the same patient<sup>29, 30, 42</sup> (see also case 12 in this paper).

### SKIN

Skin manifestations are noted frequently in some series and rarely in others. Weitz<sup>12</sup> says that most of his 88 cases (from polar bear meat) had a rash; and Spink and Augustine<sup>32</sup> record a skin eruption in 5 of 35 cases. On the other hand, in 35 sporadic cases—ambulatory and hospitalized—which we have recently seen at the Lenox Hill Hospital, there is no record of a rash or eruption in a single one. Among the 35 Boston cases two patients had a scarlatiniform rash, two had a rash "resembling rose spots," and one had an erythema multiforme. In Weitz' series most of the patients had an exanthem resembling that of measles or scarlet fever, usually beginning during the third week of the illness. A scarlatiniform enanthem with a "strawberry tongue" sometimes occurred as well.

McNaught<sup>46</sup> has recently reported the occurrence of subungual "splinter" hemorrhages. The observation of this phenomenon was made by Briggs, who noted it in "at least 12 of the last 20 cases" seen by him.<sup>47</sup> "The hemorrhages are the same as those occasionally seen in subacute bacterial endocarditis, only much more numerous. They are absolutely without pain."<sup>47</sup> These splinter hemorrhages probably represent emboli composed of trichina larvae.

## GENITO-URINARY TRACT

The kidneys occasionally show involvement, as manifested by finding albumin and casts in the urine. These findings are probably merely the result of toxic changes, although larvae have been found in the kidneys at autopsy. I have found no reference to the occurrence of a true acute hemorrhagic nephritis in this disease. At autopsy there may be "congestion, edema, cloudy swelling, and tubular degeneration."<sup>10</sup> The larvae have not been found in the urine, nor in the musculature of the ureters or bladder. Inflammation of the ureters and bladder does not occur, and the genital organs also escape infection, so far as I am aware.

## PARENCHYMATOUS ORGANS

The liver shows fatty changes at autopsy,<sup>34</sup> and the larvae have been found therein.<sup>30</sup> There are no references to hepatitis or jaundice during the course of trichiniasis. The spleen is frequently enlarged, but no distinctive postmortem changes are reported, other than "parenchymatous degeneration."<sup>10</sup> Larvae have been seen in the pancreas at autopsy,<sup>30</sup> but pancreatitis has not been described as occurring clinically. Although the embryos have been found in the bile, cholecystitis does not occur.

## ORGANS OF SPECIAL SENSE

In the eye muscles the larvae are often embedded, causing various eye abnormalities, as mentioned previously. The larvae have been found in the retina.<sup>48</sup> Permanent damage to vision has never been reported, to my knowledge. Otitis media has occurred as a complication of trichiniasis.<sup>12</sup> The semicircular canals may apparently be involved, either by toxins or by the presence of larvae, as vertigo and tinnitus occur on occasion. I have read of no cases of deafness resulting from this disease. Although the muscles of the tongue are sometimes affected, the sensation of taste does not seem to become impaired.

## BONE MARROW

A mild infection with trichinae stimulates the production of eosinophilic myelocytes and mature eosinophiles in the bone marrow; but a severe infection, especially a fatal one, causes a destruction of the eosinophilic cells, as was found many years ago by Opie.<sup>49</sup>

## LYMPH NODES

The mesenteric lymph nodes show enlargement, an accumulation of eosinophiles, and occasionally the presence of the larvae, especially in the early stages of the disease.<sup>30, 31</sup> The tracheo-bronchial nodes are similarly affected, although to a lesser degree. Most of the other lymph nodes do not show these changes.

## MISCELLANEOUS

Larvae have been found in excised mammary gland tissue, human milk, and placenta.<sup>24, 28</sup> No distinctive pathological changes have been reported in the thyroid, parathyroids, pituitary, or adrenal glands. Nor in the joints, synovial membrane or fluid, fatty tissue, salivary glands, hair, teeth, or bones, other than in the marrow.

## PHYSICAL EXAMINATION

The findings on physical examination in trichiniasis are extremely variable, as would be expected from the description of the symptomatology and pathological findings. Evidence of fever, such as warm, moist and flushed skin, and tachycardia are often present. Edema of the eyelids is one of the most constant signs. Conjunctivitis, congested sclerae, subconjunctival hemorrhages are frequently noted. Paresis of the eye muscles is more rare, but may be very misleading, especially if associated with stiff neck and painful neck muscles. Papilledema is noted in some patients who have cerebral edema. Tenderness and occasionally edema of skeletal muscles, especially the gastrocnemii, biceps and triceps, are very common findings. Congestion of the pharynx is noted rather frequently. Abdominal tenderness, sometimes marked, may be localized to any portion of the abdominal wall, and may be the source of considerable confusion in diagnosis. Enlargement of the spleen was recorded on admission in 9 of 21 cases in our hospital. In a series of 10 cases reported by Reifenstein, Allen and Allen,<sup>50</sup> four patients had a palpable spleen during the third week of the illness, while in seven the spleen could be felt five months after the onset of the illness. Reflex changes of all sorts, especially a positive Kernig sign and absent knee jerks, are common. Somnolence, delirium, coma, mental depression and disorientation are occasionally seen. Evidence of neuritis occurs rarely. Dyspnea, cyanosis, paralysis of the respiratory muscles are noted in unusual cases. Cough and expectoration, as well as signs of bronchitis, bronchopneumonia or lobar consolidation, pleurisy or pleural effusion, may be present. Rashes simulating the rose spots of typhoid or the eruption of measles, scarlet fever, German measles, or erythema multiforme have been recorded.<sup>12, 82</sup> A scarlatiniform enanthem and a "strawberry tongue" have been seen.<sup>12</sup> There may be hypotension, and the heart sounds may be of poor quality. In severe cases, in which there has been much diarrhea, one may detect evidence of dehydration, acidosis, and weight loss. There is frequently high fever and the patient may present the appearance of marked prostration and toxemia. Hemiplegia or loss of power of an arm or leg have been reported<sup>17, 20, 39, 41</sup> (case 12). Tetany (case 2) and choreiform movements have been noted.

## LABORATORY EXAMINATIONS

There are numerous laboratory procedures which will suggest, help to confirm, or definitely prove the diagnosis of trichiniasis; and in this disease

the laboratory is of particular aid in supplementing the history and physical examination. The trichina larvae have frequently been found in the blood and spinal fluid; rarely in the stool; and as a curiosity in the bile, milk of a nursing woman, pleural exudate, and pus from a furuncle. In the blood the larvae are discovered by diluting 5 to 10 c.c. of venous blood with 10 times its volume of 2 per cent acetic acid, centrifuging, and examining the sediment. The larvae are easily recognized, being  $125\ \mu$  long and  $6\ \mu$  broad, and not likely to be confused with any other structures. One may find them in the spinal fluid by merely centrifuging the fluid. Evers<sup>51</sup> points out that larvae are present in the spinal fluid in many cases, regardless of the presence of neurological signs. The spinal fluid, when larvae are present, will usually show increased pressure and increased cells—mostly lymphocytes up to 40 to 240 per cubic millimeter. Even when embryos are not present, there may be an increase in the pressure and in the number of cells. The larvae are best found in the stools by making them alkaline and waiting 12 to 24 hours before examining the liquefied stool.<sup>24</sup> According to Salzer<sup>33</sup> the feces are usually clay-colored, as a result, he surmises, of a reduction of bilirubin by the living trichinae. Others have not noticed or mentioned clay-colored stools.

#### BLOOD CELLS

The blood examination in trichiniasis is extremely important and interesting. The red blood cells and hemoglobin are not usually affected during the illness; and the main changes are in the white blood cells. There is usually a leukocytosis, sometimes to a very high figure. One of our cases had 36,000 white blood cells, which seems high until one reads of a case of van Cott and Lintz's<sup>23</sup> which had 75,000. The average figure is about 12,000 to 18,000. On the other hand there may be a leukopenia, relative or absolute, especially frequent in children. One of our cases, for example, had a total leukocyte count of 4,000 with a temperature of  $101^{\circ}$ , and another had 6,000 with a temperature of  $105^{\circ}$ . There is usually an absolute and practically always at least a relative increase in the granular cells (which include the eosinophiles). An outstanding characteristic of the smear is a moderate to marked increase in the percentage of immature polymorphonuclear leukocytes—the so-called "shift to the left," which may be quite noticeable, even up to 50 per cent, although the average is about 25 to 35 per cent.

The most important, constant, interesting, and diagnostic laboratory finding is the eosinophilia. It may reach astounding figures, such as 83 per cent in a case of van Cott and Lintz's, and 81 per cent in a case I saw several years ago in the New Haven Hospital. Drake, Hawkes, and Warren<sup>18</sup> report one patient with a total of 34,000 white blood cells and 70 per cent eosinophiles, and van Cott and Lintz speak of one with 75,000 white blood cells and over 60 per cent eosinophiles. There are a few other con-

ditions in which such extreme figures may be seen: other parasitic infestations, such as *Tenia echinococcus*; some allergic conditions, such as angio-neurotic edema; eosinophilic leukemia; periarteritis nodosa; and familial eosinophilia. But it is most unlikely that any of these diseases would cause confusion in the diagnosis of a case of trichiniasis; and it is well to remember that trichiniasis is the only disease which shows an eosinophilia during the acute febrile stage, with the exception of allergic asthma and infectious mononucleosis, and the extremely rare cases of eosinophilic leukemia and periarteritis nodosa. Of course lesser degrees of eosinophilia—5 to 25 per cent—are frequently seen in diseases other than those already mentioned. Among these are: all other intestinal helminth infestations; allergic diseases, such as pollenosis, urticaria, serum sickness, and above all asthma; skin diseases, such as pemphigus, psoriasis, secondary syphilis, and eczema, especially of the allergic type; the convalescent stage of some acute infections, such as scarlet fever and rheumatic fever; Hodgkin's disease, in which the eosinophilia may occasionally rise to very high values; and some miscellaneous conditions, such as nirvanol sickness, polycythemia vera, after certain drugs in sensitive persons, and after foreign protein injections at times.

What is the mechanism of the eosinophilia in all these varied conditions? It seems to be essentially a stimulation of the eosinophilic myelocytes of the bone marrow by certain proteins or protein breakdown products formed in the tissues. As Whitby and Britton<sup>52</sup> say: "The stimulation of eosinophils by protein affords a reasonable although a not yet complete explanation of most of the processes which have been found to cause the phenomenon of eosinophilia. . . . It seems probable that post-febrile eosinophilia is the result of stimulation of the bone marrow by the protein products set free during the process of inflammation. So long as the inflammatory process is in existence eosinophil production is depressed, but once the acute toxic stage is over, then the marrow is able to react to the stimulus of the protein products resulting from the inflammatory process." Opie<sup>49</sup> showed many years ago in guinea-pig experiments that the administration of trichinae stimulates an active multiplication of the eosinophilic myelocytes and mature eosinophiles of the bone marrow with subsequent blood and tissue eosinophilia. This occurs at a time when the larvae are being transmitted from the intestinal mucosa through the blood stream into the muscles and other tissues. A breakdown protein product is probably formed by the interaction of the larvae and the muscle proteins, which acts as the stimulus to the multiplication of the bone marrow eosinophilic elements.

The first reference in the literature to the eosinophilia of trichiniasis is that of Brown<sup>53</sup> in 1898, who found a marked increase in the percentage of these cells in the blood of three patients on the wards of the Johns Hopkins Hospital. The discovery probably came at this time because differential blood smears were becoming increasingly more common since the intensive work of Ehrlich on blood cell morphology and staining in the years following 1879.

What constitutes blood eosinophilia in humans? Drake, Hawkes, and Warren set the upper limit of normal at 500 per cubic millimeter (10,000 white blood cells with 5 per cent eosinophiles). Spink and Augustine set 400 as the limit. I cannot agree with either group that there is a definite figure, as it seems to me that the percentage is considerably more important diagnostically than the total. Thus a leukocyte count of 18,000 with 3 per cent eosinophiles, giving an absolute figure of 540 per cubic millimeter, I would not call a definite eosinophilia; conversely a total leukocyte count of 4,000 with 6 per cent eosinophiles, giving an absolute figure of only 240 per cubic millimeter, I would call a definite eosinophilia. An eosinophile count of 4 per cent I consider suspiciously high and as the upper border of normal, and 5 per cent abnormally high, irrespective of the total leukocyte count.

In animal experiments the eosinophilia of trichiniasis does not appear until the muscles are invaded.<sup>49</sup> This seems to be the case clinically as well, since the eosinophilia usually begins during the second week of the illness, which is the period when the larvae are being disseminated through the body. Aldridge<sup>54</sup> mentions two cases in which the eosinophilia developed on what seemed to be the fourth and ninth days after the ingestion of trichinous meat. Sometimes the increase may not be noted until the third week or later.<sup>32, 55</sup> Some cases have a low eosinophile count, a sudden drop, or no eosinophiles whatever throughout the illness, although these are very rare occurrences. In fatal cases there is usually a complete absence of eosinophiles, especially if the course of the disease is rapid. Aldridge described two such cases, Spink and Augustine one, Sobel one, and others have been reported. Opie found experimentally that in severe and fatal infections with trichinae there is a degeneration and destruction of the bone marrow eosinophilic elements. Complicating secondary infections will cause either a delay in the appearance of the eosinophilia or a drop in the percentage, if it was previously elevated. Drake, Hawkes, and Warren report a count of 34,000 leukocytes with 70 per cent eosinophiles in a child when he was afebrile and apparently convalescing. Two days later he developed a cough and fever, and the count then was 31,600 white blood cells with 8 per cent eosinophiles—a decrease in these cells from 23,800 to 2,500 per cubic millimeter. They mention another case, a male of 40 years, who had 12,000 white blood cells with 24 per cent eosinophiles, who, shortly after—on the day of death—had 16,800 white blood cells with but 1 per cent eosinophiles. On the other hand the same authors note the unusual occurrence of a count of 23,100 white blood cells with 38 per cent eosinophiles in a woman of 45 on the day of her death from pneumonia. Spink<sup>56</sup> found that in trichinized animals secondarily infected with bacteria the number of circulating eosinophiles is decreased, but that heat per se does not cause a reduction. A lack of eosinophilia may be noted not only in severe and fatal cases, but also under the following conditions: in patients with secondary infections; at a very early stage in the disease; possibly in an occasional individual whose bone marrow does not

respond in the usual manner, such as one who is suffering from lymphatic leukemia; and finally when there are technical errors in the blood smears. This last may sound like an academic point, but sometimes it is of practical importance and the cause of confusion in diagnosis, as I have observed on several occasions. Freshly made solutions of Wright's stain are usually too alkaline and bring out the eosinophilic granules poorly; and these weakly stained granules may lead the inexperienced to classify these cells as neutrophils. It is well to remember that eosinophilic granules are best brought out by a short period of staining; i.e., leaving the water on the slide for only about 45 seconds. If the Wright's or other polychrome stain has been poorly made, it may give totally misleading results so far as eosinophilia is concerned.

Fluctuation in the eosinophilia in trichiniasis may at times be marked, changing from a high percentage to a low one or vice versa in a few days. There seems to be no definite relation between the severity of the illness and the height of the eosinophilia, except that, as mentioned before, the very severe and fatal cases usually show a low percentage or no eosinophiles at all. Some mild or asymptomatic cases have a count of 40 to 50 per cent; a case of moderate severity may have 15 per cent or 60 per cent; a severe case may have 70 per cent or none. As an example of the fluctuations that may occur in a short time, one of our cases had an eosinophilia of 31 per cent on admission after two days of symptoms; four days later this rose to 63 per cent; in another seven days this had fallen to 40 per cent; and finally after another seven days to 12 per cent. Weitz<sup>12</sup> says that there are two peaks to the eosinophile curve: one at the beginning of the illness and another at about the time the patient has convalesced enough to leave the hospital. Although this occurs in some patients, it is by no means the rule. There is considerable difference of opinion concerning the question of how long the eosinophilia lasts. I have collected a group of cases from various articles<sup>17, 35, 42, 50, 57, 58, 59</sup> (and my own series) in which differential counts were done at various times after the onset of the illness. In 44 cases the highest eosinophilia early in the disease averaged 34 per cent. In 21 of these cases in which counts were performed three months later, the average had fallen to 12 per cent, with none as high as the initial maximum. There were 10 patients who had smears made about 4½ months after the beginning of the infection, and these counts were on the average about one-sixth of the initial average high: 6 per cent. Thirteen counts were repeated six months from the onset and averaged 5 per cent, with only one above 9 per cent. At 8 to 12 months 12 cases all showed 5 per cent or less and averaged 2.5 per cent, which is within normal limits. In summary it may be said that most cases will show only a slight eosinophilia—5 to 6 per cent—six months after infestation, and that practically all will have normal figures after 8 to 12 months.

## SEDIMENTATION RATE, BLOOD CHEMISTRY, WIDAL TEST

Determinations of the erythrocyte sedimentation rate in trichiniasis have not been recorded in the literature. Unfortunately, this determination was made in only four of our cases. The results in two were well within normal limits, in one the rate was slightly increased, and in one it was moderately increased. All of these patients had fever and were acutely ill with uncomplicated cases at the time the sedimentation rate was determined. While four cases is too small a number from which to draw conclusions, it would seem that a marked increase is not the usual finding, even during the acute febrile stage.

The blood chemistry values are within normal limits in most uncomplicated cases.<sup>60</sup> Some observers have claimed that there is a decrease in sugar tolerance, but a review of the work is not at all convincing; and all our patients who had fasting blood sugar determinations showed normal values. The one type of blood chemistry abnormality which one may expect to encounter is that associated with vomiting, diarrhea, and dehydration; i.e., lowered CO<sub>2</sub> combining power, slight increase in the non-protein nitrogen, and occasionally evidence of loss of fixed base, such as a low serum calcium or sodium.

The Widal test may occasionally be positive, even in high dilutions.<sup>55</sup> This may sometimes be a source of confusion, as will be pointed out later.

## INTRADERMAL AND PRECIPITIN TESTS

In 1928 Bachman<sup>61</sup> described an intradermal test for trichiniasis. Trichina larvae obtained by digestion of infected meat are desiccated, and the powder is prepared in dilutions of 1:500 and 1:10,000 with Coca's solution. 0.01–0.05 c.c. is injected intradermally and the reaction is read in 15 to 30 minutes. A positive reaction is similar to that produced by other allergens with intracutaneous testing; i.e., a wheal with or without pseudopodia, a surrounding zone of erythema, warmth, and sometimes itching. The test is much more specific when done with a 1:10,000 dilution, and this is the strength which should be used in order to get a minimum of false positives. The investigators<sup>21, 58, 62, 63, 64</sup> who have had the most experience with the test feel that it is a definite aid in diagnosis, especially when a negative reaction early in the disease turns positive during the course of the illness. There is a theoretical possibility that repeated tests with the antigen might provoke a falsely positive result in a person not suffering from trichiniasis. Repeated intradermal injections of the antigen into a small group of doctors showed the author that negative tests do not thereby become falsely positive.

A negative test is more useful in ruling out trichiniasis than is a positive one in establishing the diagnosis. A positive test may result from trichinous infestation many years before,<sup>58</sup> from other parasitic infestations,<sup>62</sup> or may



be found, although rarely, in persons who give false-positive reactions to all intradermal tests. Schapiro, Crosby, and Sickler<sup>64</sup> found a close correlation between the skin test findings and the postmortem findings in a large series of cases. One drawback of the intradermal test is the fact that it does not become positive, as a rule, until between the fourteenth and twentieth days of illness; sometimes not until even later; and occasionally not at all. Until recently it was difficult to obtain the antigen, but now one can get vials of the 1:10,000 dilution from the National Institute of Health.

The precipitin test is at least as accurate as the skin test,<sup>32</sup> develops slightly later—about the fourth week—and may also remain positive for many years.<sup>58</sup> In a recent series of 44 hospitalized cases of trichiniasis, 100 per cent gave positive intradermal and precipitin tests.<sup>21</sup> Serum may be sent to the laboratory of the National Institute of Health for the precipitin test.

### BIOPSY

The biopsy is an inconvenience to the patient, but it is not a dangerous procedure and usually does not prolong the hospital stay very much. Evers<sup>51</sup> suggests examination of a centrifuged specimen of spinal fluid whenever biopsy is contemplated, since finding the larvae in the fluid will obviate the necessity of an operation. Biopsy is of some importance in the final diagnosis, although even when it is negative, one may be entirely justified in making the diagnosis of trichiniasis on clinical grounds. But a positive report will definitely confirm the diagnosis. Hall<sup>6</sup> pointed out that the tissue excised should be examined as a press preparation rather than as sections, since the former is more certain and rapid. More recently Queen<sup>65</sup> recommended the digestion in artificial gastric juice of biopsy and necropsy material and suspected meat products.

In our series there were 15 positive biopsies out of 17 performed, a fairly high percentage. It must be said, in all fairness, that almost all of the 15 positive cases had been rather definitely diagnosed as trichiniasis before the operation, and that the two patients with negative biopsies are still considered by us as definite cases. So I cannot agree with those who say that the biopsy is of extreme importance, but am more of the opinion of Spink and Augustine,<sup>32</sup> who believe that "the biopsy is an unnecessary procedure, not only because of the uncertainty of finding the parasites in a small piece of muscle, but also because the precipitin and skin tests are as reliable as the procedure of biopsy, which is, of course, an inconvenience to the patient." However, the skin and precipitin tests are not by any means infallible, and may be positive from a trichinous infection long before the present illness. Finally, while Spink and Augustine and also Sobel say that the larvae may be missed in a biopsy, actually the biopsy was reported as positive in 12 of 13 cases in Spink and Augustine's series and in 6 of 7 in Sobel's, for a total of 90 per cent correct positives, which is a very good record for any laboratory procedure in medicine.

## DIAGNOSIS

The diagnosis of trichiniasis is frequently a difficult matter, and the percentage of correct diagnoses on first seeing the patient is not high. In the 35 cases in the Boston series,<sup>32</sup> the preliminary diagnosis after the history and the physical examination, but before any laboratory data were obtained, was right in only 11 cases or 31 per cent. In our series, trichiniasis was definitely diagnosed on admission, before obtaining the blood count, in 7 of 21 patients or 33 per cent, although the disease was mentioned in the admission note as a possibility in 5 others or in an additional 24 per cent. Hall<sup>6</sup> has pointed out that "the classical picture as given in the textbooks is greatly oversimplified and represents only a composite picture." The typical case is not often seen; and trichiniasis is characterized by the lack of regularity of its manifestations and course. As in many other obscure diseases, merely thinking of the possibility will help considerably in arriving at the diagnosis. Then one must take a careful history, with specific questioning relative to any recent ingestion of pork products. Inquiry must be made concerning any recent illness suggestive of trichiniasis in other members of the family.

Suspicious symptoms are: edema of the eyelids, which should cause one to consider a diagnosis of trichiniasis until the edema is proved to be due to some other cause; muscular pains, fever, nausea, vomiting, generalized abdominal pain, diarrhea or constipation, chills and sweats, headaches, diplopia, pain and redness and burning in the eyes, dyspnea and other pulmonary symptoms. Important points in the physical examination are: edematous eyelids, muscular tenderness and swelling, fever and tachycardia, conjunctivitis and subconjunctival hemorrhages, paresis of the eye muscles, abdominal tenderness, enlarged spleen, signs of meningeal irritation and of encephalitis, evidence of dehydration, hypotension, and signs of pulmonary congestion or consolidation.

The most suggestive laboratory finding, and in fact, the thing which most often calls one's attention to the correct diagnosis, is the eosinophilia. A very important confirmatory finding is an eosinophilia in other members of the family, especially if it is accompanied by suggestive signs and symptoms, and if there is no allergic history to explain the eosinophilia. The total leukocyte count and the shift to the left are not very helpful diagnostically, except when considered in conjunction with the eosinophilia. The intradermal and precipitin tests are of considerable aid, but become positive only many days after one would like to make a diagnosis. Final proof of the diagnosis depends on finding the larvae in the blood, spinal fluid, or in a piece of muscle at biopsy. Spink and Augustine feel that "the most reliable diagnostic aid is the eosinophilia." With this I agree, if one is speaking of the presumptive clinical diagnosis. Final proof cannot depend only on an eosinophilia, of course. Blumer<sup>26</sup> says: "Any febrile disease which is accompanied by edema of the eyelids and evidence of involvement of the muscles

at once calls for a blood count." I would go further and suggest that any obscure illness warrants a differential blood smear, repeated several times, if necessary. Finally it should be borne in mind that a negative biopsy, the failure to find the trichina larvae in the blood, spinal fluid, or stools, a negative skin or precipitin test, or the absence of eosinophilia does not rule out the diagnosis of trichiniasis.

### DIFFERENTIAL DIAGNOSIS

One of the most interesting and amusing aspects of the study of trichiniasis is the astounding variety of diseases with which it has been confused. Rather than merely listing the conditions which have been diagnosed by mistake, it will be more instructive to group them according to the symptoms or signs which caused the error. The gastrointestinal manifestations, with nausea, vomiting, diarrhea, and abdominal pain, which are so common early in the disease, may simulate: infectious gastro-enteritis, ptomaine or food poisoning, "intestinal influenza," colitis of various types, dysentery, and even cholera.<sup>6, 32</sup> The fever, especially when associated with muscle pains as it usually is, may cause one to diagnose gripe or influenza. When the fever is very high and the course of the illness fulminating, septicemia may be suspected, as in one of our cases (number 2). When the fever is prolonged, undulant fever and pulmonary tuberculosis have been considered.<sup>32</sup> A common error, especially in former years, was to call the illness typhoid fever, which is quite understandable in view of the occurrence at times of high sustained fever with no localizing signs, bradycardia, enlarged spleen, positive Widal test, and even an eruption resembling rose-spots—although all these in the same patient would be distinctly unusual<sup>37, 41, 55</sup> (case 5 in this paper). Sometimes the hospital chart is signed out as "Fever of Unknown Origin"<sup>66</sup> (case 10).

The edema of the eyelids has often resulted in an initial diagnosis of acute nephritis or acute sinusitis, and more rarely of angioneurotic edema, especially because of the associated eosinophilia<sup>16, 32</sup> (cases 6 and 9). The edema of the masseters has on occasion suggested a diagnosis of mumps<sup>54, 50</sup> (case 3). Myositis, especially when combined with fever, causes considerable confusion. Rheumatic fever and acute generalized arthritis of various kinds are often mistakenly diagnosed. Involvement of the masseter muscles has caused physicians to decide that the patient was suffering from tetanus.<sup>16, 32</sup> When the abdominal muscles are attacked, bizarre and often serious errors of diagnosis may ensue. Acute appendicitis<sup>66</sup> or an "acute surgical abdomen" may be suspected, and an unnecessary operation may be performed. A less serious error is the tentative diagnosis of gall bladder disease<sup>6</sup> or peptic ulcer.<sup>55</sup> With myositis in the back, renal colic has been simulated (case 4 and another unreported case in our series). Any other type of colic may likewise be erroneously diagnosed.

Neurological signs and symptoms occur frequently enough to cause con-

siderable confusion, and the following have been diagnosed at various times: poliomyelitis, especially when there is associated muscle pain and weakness; encephalomyelitis and encephalitis,<sup>39</sup> which may actually be present due to the trichina larvae; tuberculous meningitis<sup>32</sup> and pyogenic meningitis<sup>38</sup>; polyneuritis<sup>12, 30</sup>; polymyositis<sup>67</sup>; periarteritis nodosa<sup>39</sup>; chorea (case 11); and cerebral thrombosis resulting in hemiplegia.<sup>26</sup>

Cardiac involvement makes one think of rheumatic endocarditis and myocarditis<sup>32</sup> (case 11), or of a myocarditis of unknown etiology.<sup>6</sup> Pulmonary signs and symptoms have resulted in the diagnosis of lobar or lobular pneumonia or pleurisy, any of which in fact may actually be present.<sup>37</sup> Other miscellaneous diagnoses have been reported,<sup>6, 32, 41, 55</sup> such as: pelvic inflammatory disease, paratyphoid fever, malaria, erysipelas, syphilis, and others.

The *commonest* incorrect diagnoses are: grippe and influenza, acute nephritis or sinusitis, typhoid fever, and rheumatic fever. When one realizes the large number of cases which are not correctly diagnosed for many days or weeks even when under close observation in the best hospitals, one wonders how many cases must be missed in mildly ill persons in private practice. Many of these overlooked cases are, I believe, labelled with that solution to the doctor's diagnostic dilemma—grippe.

### PROGNOSIS

The prognosis in trichiniasis, as in other diseases, depends on a number of factors. First, although probably not most important, is the number of trichinae in the infected meat and the amount of meat eaten. Perhaps achlorhydria is a favorable condition for the patient; in fact, it is conceivable that the disease will not develop in such individuals, as the capsule around the larvae may not be digested with a liberation of live trichinae. Early vomiting and diarrhea are theoretically favorable events, as then fewer larvae will remain in the intestinal tract. However, it seems that this must be a minor point when one considers how very many larvae (about 1,000) develop from each adult female. Another consideration is the general health and resistance of the host, although this is naturally a difficult matter to assess. To my mind, by far the most important element in the prognosis is the fortuitous *localization* of the larvae. In the gastrointestinal tract, a severe diarrhea with its resulting dehydration and blood chemistry disturbances, may be a large contributing factor to a fatal outcome. In the musculature, a great deal depends on which muscles are affected and to what extent. A myositis with edema or paralysis of the diaphragm, intercostals, muscles of the glottis, larynx and trachea, and those of mastication and deglutition, adds greatly to the danger of the disease. Patients may die of respiratory paralysis as a result of such a localization. If the cardiac musculature is involved, the prognosis is obviously worse than if the heart is spared. Migration of the larvae into the brain is serious, and the mor-

tality in cases with encephalitis is high, as would be expected. Pulmonary involvement with pneumonia and pleural effusion naturally adds to the gravity of the condition. Why the larvae localize in different organs and tissues in various individuals is no more known than why organisms do the same thing in bacterial diseases.

Aside from the above considerations, one must take into account the degree of dehydration and acidosis; the amount of toxicity; perhaps the height of the temperature; and finally the complications. There may rarely be hemorrhages, especially cerebral, gastrointestinal, and pulmonary; abscess formation; secondary bacterial infections, etc. A fatal peritonitis complicating trichiniasis has been reported.<sup>41</sup> Barrett and Sears<sup>17</sup> saw three cases of acute appendicitis occurring during attacks of trichiniasis. The only laboratory determination of value prognostically, aside from the blood chemistry derangements that may be present, is the degree of eosinophilia. If the eosinophiles are very low or absent or falling suddenly, a serious condition is usually present; otherwise the total or percentage of these cells means nothing prognostically.

### TREATMENT

The treatment may be divided into three aspects: specific, symptomatic, and convalescent care. Chemotherapy has been tried with very little success and has been almost entirely discarded. The most used chemical in former times was silver arsphenamine<sup>68</sup>; but the results were not impressive. Miller, McCoy, and Bradford<sup>69</sup> conducted a series of well-controlled experiments on rabbits in 1932, which dealt a severe blow to the claims of the chemotherapeutists. They found that the intravenous injection of neo-arsphenamine, antimony potassium tartrate, acriflavine, rivanol, gentian violet, metaphen, and Lugol's solution had no effect whatever on the disease, and concluded that "the therapeutic rationale of the injection of such drugs in the treatment of trichiniasis is questionable." More recently McCoy<sup>70</sup> found sulfanilamide of no value in trichinous rats. Perhaps it is fortunate that a parasiticide has not been discovered, since one must consider the possibility of severe embolic or allergic phenomena following a rapid destruction of large numbers of trichinae, as suggested by van Someren<sup>71</sup> in his recent authoritative review of the treatment of trichiniasis.

The use of human convalescent serum was recommended by Salzer<sup>24, 33</sup> as early as 1916, and he saw what he considered some good results with it. In spite of the claims of Schwartz,<sup>72</sup> based only on animal experiments, that convalescent serum is of no value, Blumer<sup>26</sup> feels that "the quest for an effective antitoxic serum offers a more hopeful solution [than chemical agents]." With this I agree, as we have seen in recent years the remarkable value of a number of different antitoxic sera. It seems likely that the toxemia of trichiniasis would respond to human convalescent serum, but that the tissue and organ changes, such as myositis, myocarditis, encephalitis,

would not respond to anything other than symptomatic treatment. Some cases are predominantly of the toxic type and warrant a further trial of serum therapy when this is available. With this statement van Someren<sup>71</sup> as well as Culbertson and Kaplan<sup>73</sup> are in agreement.

Wantland<sup>74</sup> reasoned that "if cyst formation and subsequent calcification could be hastened, this would shorten the critical period in trichinosis and more quickly terminate the disease. The treatment of trichinous rabbits with irradiated ergosterol and calcium lactate has a definite therapeutic value. It remains to be tested in human cases of trichinosis." In a later article<sup>75</sup> the same author showed that calcification of the cysts in trichinized rats could be hastened, but admits that ergosterol in the necessary large doses is definitely toxic. Brand, Otto, and Abrams<sup>76</sup> recently showed that "calcification of trichina cysts parallels calcification in other host tissues." And with wise clinical judgment they conclude: "We feel then that any attempt at forced calcification as a therapeutic measure in trichinosis is not only futile with the usual human dose of parathormone, irradiated ergosterol, or related substances, but that any serious attempt to increase the doses of such substances to calcifying levels would be exceedingly dangerous."

Symptomatically one should first of all confine febrile patients strictly to bed, as emphasized by Anderson.<sup>13</sup> An initial cathartic should be given if the case is diagnosed very early while the larvae are still in the intestinal lumen. Usually, however, the diagnosis is not made until the larvae have burrowed into the mucosa, at which time a cathartic is of no value. Vermifuges have received little attention, but do not seem promising for the same reason. However, van Someren<sup>71</sup> recommends the clinical trial of Butolan, an anthelmintic, especially during the first two or three weeks of the disease. Diarrhea may be severe enough to require opium, although usually bismuth salts and kaolin suffice. Large amounts of fluid are indicated to help overcome the toxemia and replace fluids lost by vomiting and diarrhea. Sodium chloride should be given freely for the same reasons and because much salt may be lost in sweating. Calcium gluconate intravenously has been used with apparently good results by Sogemeier<sup>77</sup> during the acute febrile stage. Muscle pains can usually be controlled with salicylates. In the presence of myocarditis, fluids should be somewhat restricted and carbohydrates increased. The symptoms of encephalitis and meningismus may be helped by spinal taps to relieve the increased pressure. In the rare cases showing paralysis of the diaphragm and intercostal muscles, a respirator may be life-saving.

In protracted cases the nutrition may be considerably disturbed, and the patient may become emaciated and anemic. In such cases iron preparations are indicated as well as some form of tonic. Of all acute illnesses, trichiniasis is perhaps the one in which the use of glycine as a convalescent tonic is most rational, as this amino acid has been shown<sup>78</sup> to enhance the capacity for muscular activity. In mild cases the patient is ill for only two to three

weeks; but in severe cases convalescence is not complete until after many months in some instances. These cases must receive a high caloric diet in addition to iron and tonics.

### SUMMARY

1. A general review of various aspects of trichiniasis is given, and the high incidence of the disease pathologically and clinically is indicated.
2. A description of the parasite and its development, the methods of human infestation, the prevention of the disease, a history of outbreaks and the mortality are discussed.
3. A clinicopathological study is presented, with special emphasis on the fact that symptoms and signs depend largely on the localization of the larvae.
4. The value of numerous laboratory examinations is assessed, and stress is placed on the diagnostic importance of a blood eosinophilia.
5. The important points in the diagnosis and differential diagnosis are emphasized, especially the occurrence of puffy eyelids and muscle pain.
6. Prognosis and treatment are considered.
7. From a series of 35 sporadic cases of trichiniasis, 12 are abstracted to illustrate various interesting points and mistakes in diagnosis.

### CASE REPORTS

#### *Case 1. Typical severe type.*

A 37 year old male. History of 17 days of severe diarrhea—20 to 25 stools daily—without blood; general abdominal discomfort; chills and fever (amount not known). Four days of very puffy eyelids with pain and burning in the eyes. Three days of pain and tenderness in the muscles of the back, chest, arms, and legs. Loss of 22 pounds in weight. Ate cooked pork about four days before onset of symptoms. On examination there were found: edematous eyelids, injected conjunctivae, palpable spleen, slight epigastric tenderness, muscular tenderness in arms and legs, and evidence of dehydration and weakness. The admission diagnosis was: Trichiniasis. The leukocyte count was 36,000 with 51 per cent polymorphonuclears (of which 17 were immature), 12 per cent lymphocytes and 37 per cent eosinophiles. The eosinophilia increased to 58 per cent on the ninth day in the hospital, decreased to 36 per cent a few days later, and to 1 per cent in eight months. The temperature ranged from 101° to 104° for three days; then from 100° to 102° for the next five days, and remained normal after that. The diarrhea was controlled within three days. Muscle biopsy was positive. The patient's wife had "grippe" at home for two weeks, and was later found to have an eosinophilia of 45 per cent.

#### *Case 2. "Septicemia."*

A 4 year old female.\* The child was well up to two days before admission when she began to complain of sore throat and abdominal pain. This was followed by vomiting, which lasted several hours. She then developed fever, ranging from 102° to 106°. Swelling of the eyelids and cheeks was noted. A 12 year old sister and a 4 year old twin brother were said to have swelling of the face and eyelids at this time. On examination the patient looked seriously ill, with a temperature of 105°, a pulse of 134, and respirations of 54. The pharynx was slightly injected. The knee jerks and biceps reflexes were absent. On the dorsum of the right hand a small

\* Cases 2, 3, 5 (second admission), 6 and 7 have previously been reported from this hospital by Sobel.<sup>10</sup>

infected, but apparently healing area was seen. The rest of the examination was negative. The admission diagnosis was: Pneumonia (?) and toxic nephritis (?). The leukocyte count on admission was 9,450 with 79 per cent polymorphonuclears (of which 47 were immature), 21 per cent lymphocytes and no eosinophiles. The urine showed a moderate amount of albumin, many hyaline and occasional granular casts, and a trace of acetone. The blood chemistry was as follows: Urea N 13.8; creatinine 0.5; uric acid 5.4; sugar 84 mg. per cent; CO<sub>2</sub> combining power 27 vol. per cent; calcium 8.5 mg. per cent. The spinal fluid, the day after admission, showed an increased pressure, but was otherwise normal in every respect. A roentgen-ray of the lungs revealed no pathologic process.

The day after admission the child became comatose; signs of meningeal irritation developed; carpopedal spasm was noted, as well as paresis of the left side of the face with unequal pupils. The edema of the eyelids became more marked. The temperature ranged from 105° to 106° for 36 hours, then began rising and reached 109° at the time of death, which occurred 48 hours after admission or four days after the beginning of the illness. The final clinical diagnoses were: toxic nephritis; meningismus; acidosis; (?) septicemia.

Autopsy was entirely negative grossly except for edema of the brain. Blood culture was known to be sterile up to the time of the autopsy. As a last resort in attempting to explain the illness and death, one of the clinicians asked the pathologist to take a piece of the diaphragm for microscopic study. This was a most fortunate inspiration, as the cause of death would otherwise probably never have been known. Unencysted larvae of *Trichinella spiralis* were found in the diaphragm. The heart showed a moderate leukocytic infiltration. The brain showed congestion of all vessels, but no trichinae were seen and there was no evidence of an encephalitis, in spite of the clinical picture. This patient seems to have had the shortest clinical course with positive autopsy findings on record, at least in the literature of the past 25 years.

#### Case 3. "Mumps."

A 14 year old female. Two weeks before admission the patient developed bilateral parotid swellings, thought by the family to be due to mumps. She also had diarrhea, lasting two days, and fever of 102° to 103° up to the day of admission, when it rose to 105°. There were vague pains in the legs, and for the past four days intermittent epigastric pain. A four year old sister (case 2) had died two days previously, but the results of the microscopic sections were not known when this patient was admitted. A four year old brother was said to be at home with fever and puffy eyelids. Physical examination: temperature 105°; pulse 116; respirations normal. The child looked acutely ill. The liver and spleen were slightly enlarged; there was questionable swelling of the eyelids and over the parotid glands, and very slight tenderness of the leg muscles. The admission diagnosis was: 1. Mumps—convalescent (?); 2. Trichiniasis (?). The leukocyte count was 6,000 with 76 per cent polymorphonuclears (of which 49 were immature), 11 per cent lymphocytes, and 13 per cent eosinophiles. The blood was negative for trichina larvae (Herrick-Janeway method). The eosinophilia increased to 40 per cent five days later and decreased to 14 per cent in another seven days. The temperature fell gradually, reaching normal on the eighth day in the hospital. Biopsy, done on the twenty-third day of illness, was positive. The "parotid swelling" was probably caused by an edema of the masseter muscles.

#### Case 4. "Renal colic."

A 35 year old female. Two weeks before admission the patient noted a swelling of the face and neck, a puffiness of the eyelids, a stiff neck, and fever. Except for the fever, these symptoms disappeared in eight days. Five days before admission she developed severe pain in the left flank, which had persisted. There was no radiation of the pain, and it was severe enough to require morphine. Severe frontal headache and occasional diplopia were present during the illness. On examination the patient



was found to be in very severe pain. The spleen was felt at the costal margin. There was tenderness, seemingly in the muscles, over McBurney's point and in the left lower quadrant. Tenderness was noted over the calf and buttock muscles and in the left costovertebral angle. The admission diagnosis was: renal calculus. The blood count, done subsequent to the diagnosis, showed a total count of 14,700 leukocytes with 49 per cent polymorphonuclears (of which 22 were immature), 22 per cent lymphocytes, and 29 per cent eosinophiles. The temperature never rose above 101.6° in the hospital. After the first blood count, the diagnosis was changed to trichiniasis, and biopsy several days later was positive. If more attention had been paid to the history and if trichiniasis had only been thought of, the diagnosis should have been apparent on admission, even before seeing the result of the blood count.

*Case 5. "Typhoid fever."*

A 6 year old female. History of three days of fever, abdominal pain, and puffy eyelids. Positive findings on physical examination: edematous eyelids and a palpable spleen. The admission diagnosis was: Pyelocystitis. The leukocyte count was 4,400 with 34 per cent polymorphonuclears, 54 per cent lymphocytes, and 12 per cent eosinophiles. Unfortunately no further counts were done. The Widal test was positive in dilutions of 1:40 and 1:80, but higher dilutions were not carried out, and the test was not repeated. The blood, urine, and feces were all negative for typhoid bacilli on culture.

The temperature fluctuated between 99° and 103° during the first week in the hospital; then during the next six weeks it fluctuated from subnormal (97° to 98°) up to 100°, with a rise to 101°-103° about once weekly. The pulse was always disproportionately high. A diagnosis of typhoid fever was made, and the chart signed out as such. Against this diagnosis are the following: an eosinophilia, a relatively low temperature lasting only 12 days, a rapid pulse, absence of rose spots, negative cultures of the blood, stools, and urine. The Widal test was done when the temperature was high, was not carried to dilutions higher than 1:80, and was not repeated. In favor of the diagnosis of trichiniasis are the history and observation of puffy eyelids. The fever, enlarged spleen, leukopenia, and positive Widal test would fit either diagnosis. The eosinophilia, even though only 12 per cent, rules out typhoid and clinches the diagnosis of trichiniasis in this case.

This patient returned to the hospital four years later at the age of ten. The history was of one day's duration with fever, pain in the muscles, pain and burning in the eyes, and headache. Examination revealed tenderness in various muscles and slight puffiness of the eyelids. There was an eosinophilia of 30 per cent, and further questioning brought out the fact that she remembered having eaten pork six weeks previously (although the pork which caused her symptoms was undoubtedly eaten subsequently). Biopsy was reported as negative; but muscle taken from her sister, a patient at the same time, contained the trichinae. The diagnosis of trichiniasis appears entirely justified in view of the history, the physical examination, the eosinophilia, and the sister's positive biopsy. This case illustrates the occurrence of reinfection in this disease, which, although rare, certainly does occur.

*Case 6. "Nephritis."*

A 10 year old female. Present illness: puffiness of the face for two days. Past history: "kidney trouble" at the age of two years. Physical examination: edema of eyelids; congested pharynx; systolic murmur at apex; temperature 102°. Admission diagnosis: Acute nephritis. Blood count the next day showed 40 per cent eosinophiles; biopsy was positive; urine was normal. Final diagnosis: Trichiniasis.

*Case 7. "Grippe."*

A 9 year old female. History of 36 hours of pain in the eyes, coryza, cough, headache, generalized body aches, fever, and puffy eyelids. Examination revealed edema of the eyelids, crepitant râles over the left lower lobe, tenderness of the muscles of the neck and legs; temperature 103°. The admission diagnosis was: grippe or broncho-

pneumonia. The first blood count, done subsequent to this diagnosis, showed 10,000 leukocytes with 63 per cent polymorphonuclears (of which 50 were immature), 31 per cent lymphocytes, and 6 per cent eosinophiles. Course: the temperature ranged from 102° to 104° for nine days with one spike to 106°. Eosinophilia later increased to 36 per cent and biopsy was positive.

*Case 8. Accidental finding—time of infestation not known.*

A 39 year old female. Admitted to the hospital with a fracture of the femur. An open reduction was done, and bone from the femur with some of the surrounding tissue was sent to the laboratory for routine examination. The pathologist's report was as follows: "Extremely sclerotic and degenerated voluntary muscle. Tissues show focal and perivascular round and plasma cell infiltration. They contain several encapsulated trichina larvae. Diagnosis: Trichiniasis."

Blood smears taken subsequently on two occasions showed 0 and 2 per cent eosinophiles. No history suggestive of trichinous infection could be elicited, and it is reasonable to assume that it occurred many years before.

*Case 9. No symptoms or signs.*

A 9 year old female. The mother of this child was a patient in the hospital with typical history and physical findings of trichiniasis and an eosinophilia of 61 per cent. This child had no symptoms or signs whatever, and yet was found to have an eosinophilia of 40 per cent, which decreased after 4½ months to 10 per cent. This case illustrates the fact that if one will investigate the members of the family of patients with trichiniasis, one will discover many more instances of the disease, either unrecognized or misdiagnosed.

*Case 10. "Acute sinusitis."*

A 9 year old male. Admitted on January 7, 1938. History: Two days of puffy eyelids, generalized abdominal pain, slight, non-productive cough, and fever up to 104°. Examination: Child looked acutely ill; temperature 103.8°; pulse 88; respirations 22. There was edema of the eyelids; the sinuses transilluminated poorly; the spleen was palpable with a very tender edge. Admission diagnosis: Acute pansinusitis. Roentgen-ray examinations: normal lungs; sinuses "fairly clear." Urine normal on several occasions. Sedimentation rate was within normal limits, even while patient had a high temperature. Blood culture and Widal test: both negative on two occasions. Blood counts were as follows:

1/7 :	WBC	13,100;	polys.	75% (21 immat.);	lymphs.	22%;	eosinos.	3%
1/10:	"	15,150;	"	73% (14 " );	"	24%;	"	3%
1/20:	"	9,650;	"	64% (15 " );	"	36%;	"	0%
1/26:	"	—;	"	58% (18 " );	"	25%;	"	17%
1/27:	"	9,200;	"	45% (6 " );	"	33%;	"	22%

I believe that the eosinophilia was probably missed during the first two weeks of hospitalization because of technical errors. The smear which showed 17 per cent eosinophiles had been stained with MacMeal's tetrachrome stain, whereas another smear taken at the same time, but stained with the Wright's stain then in routine use, showed no cells with granules red enough to allow the cells to be identified as eosinophiles with assurance. This has happened on several occasions to my knowledge, and it may account for some of the cases in the literature with a low or absent eosinophilia.

After the patient's temperature had varied from 102.0° to 105.4° for four days in the hospital, it gradually fell to normal. The temperature-pulse curve resembled that of typhoid, which was strongly suspected at first. For a while the muscles were so tender that the child could scarcely move because of pain. Biopsy taken four weeks after the onset of the illness was positive for trichinae. Additional questioning brought out the fact that one week before the onset, the family had eaten some smoked ham without further cooking. The father had had muscle pains, diarrhea, and fever at home, and was later found to have 39 per cent eosinophiles.

*Case 11. "Fever of unknown origin."*

A 40 year old female (mother of case 10). Admitted December 30, 1937. For 10 days before admission this patient had had high fever, up to 104.0°. Sweating and chills were prominent. Headache and generalized body aches and dull abdominal cramps with constipation were present. She vomited once the day before admission. Family history: her husband was ill at home with chills and fever. On examination she looked acutely ill; there was pallor and the tongue was coated. The temperature was 103.6°; pulse 100; respirations 26; blood pressure 92 systolic and 68 diastolic. The spleen was not felt. There was no muscle tenderness and no lymphadenopathy. The rest of the examination was also negative. On admission the diagnosis was deferred.

Blood studies showed the following: on admission, the leukocyte count was 18,000 with 76 per cent polymorphonuclears (of which 28 were immature); 22 per cent lymphocytes; 2 per cent eosinophiles. Four days later the leukocyte count was 18,350 with 90 per cent polymorphonuclears (of which 27 were immature); 9 per cent lymphocytes; 1 per cent eosinophiles. Laboratory examinations, including cultures of the blood, urine, feces, and agglutination tests for typhoid, paratyphoid, and undulant fever, were all negative. Roentgen-rays of the lungs showed no lesions. Course: the temperature fluctuated between 99.0° and 105.6° for six days, and then stayed below 100°; the pulse varied from 88 to 96, which was low compared to the temperature. Physical examination continued to be essentially negative. The patient was discharged after 15 days in the hospital. The final diagnosis was: "Fever of Unknown Origin."

She returned 10 days later with a history of having had diarrhea (5 to 10 stools daily), starting just after leaving the hospital. She did not think she had had fever, but the temperature had not been taken. There were no chills or other symptoms. Examination was essentially negative again. The diarrhea continued for four days. The temperature was normal. The various agglutination tests were again negative. The blood counts were as follows:

1/23: WBC 13,500; polys. 39% (3 immature); lymphs. 37%; eosinos. 24%.

1/26: WBC —; " 76% (4 " ); " 24%; " 0.

1/26: (later same day using tetrachrome stain): Eosinophiles: 33%.

2/4: WBC 17,100; polys. 43%; lymphs. 20%; eosinos. 37% (after 2 weeks of normal temperature).

Biopsy done seven weeks after onset of the original symptoms was positive.

Comment: Here again I feel that the eosinophilia was overlooked because of a poor Wright's stain, at least on the examination of 1/26, on which date another smear stained with MacMeal's tetrachrome stain showed 33 per cent eosinophiles. Whether or not the patient actually had more than the 2 per cent eosinophiles recorded on the first admission is a moot question, but I am inclined to believe that she did.

*Case 12. "Encephalitis" or "Chorea and Rheumatic Heart Disease."*

A 32 year old housewife. Admitted with a history of two weeks' dry cough, with soreness of the abdominal muscles, which she attributed to the strain of coughing. For a period of five days about a week before admission she had had 5 to 6 watery, brown stools, without blood or mucus, daily. Palpitations were noted for the past 10 days. Loss of power of the right hand and arm was a prominent symptom during the past week, and pain and tenderness of the finger tips of both hands for the past few days. During the two days prior to hospitalization she noted a failing memory and a lack of power of concentration. Past history: Appendectomy at 17 years; articular rheumatism seven years before at the age of 25; tonsillectomy at 27. On examination she presented the following picture: temperature 101.6°; pulse 108; respirations normal. She appeared acutely ill and pale. There were athetoid movements of the head, arms, and legs. A loud systolic murmur was heard at the

apex and at the base. The blood pressure was 118 systolic and 88 diastolic. The cardiac rhythm was regular. The reflexes were normal except for the absence of the abdominals. There was an inability to coordinate. The admission diagnosis was: Encephalitis or chorea with active rheumatic heart disease. The leukocyte count was 18,500 with 80 per cent polymorphonuclears (28 immature), 18 per cent lymphocytes, 2 per cent basophiles, 0 eosinophiles. The sedimentation rate was moderately increased. The Wassermann test was negative, as were several urine examinations. Roentgen-ray of the lungs revealed no lesions. The spinal fluid was under no increased pressure, was clear and had 10 leukocytes and 50 erythrocytes per cubic millimeter; the protein was 53 and the sugar 69 mg. per cent. Wassermann and colloidal gold curve were negative. An electrocardiogram on admission showed a rate of 83; PR: 0.22; QRS: 0.08. Lead I: S slurred and notched; T low. Lead II: T diphasic. Lead III: T inverted. Later tracings showed a gradual return to normal, but with constant inversion of T in Leads II and III.

Course: The temperature varied from 99.0° to 101.0° for 10 days; then it remained normal. Three days after admission a neurological consultation was recorded as follows: "Paralysis of convergence and accommodation; right cerebellar asynergia; absent abdominals; mental torpor; bilateral papilledema. Diagnosis: Encephalitis of unknown etiology." The patient needed catheterization for a number of days. There was a gradual improvement in the general condition, although the ocular signs remained. After 10 days in the hospital a repeat blood count, the first since the admission count, showed 50 per cent eosinophiles, and four days later there were 51 per cent. After the eosinophilia was discovered, the etiology of the encephalitis and myocarditis was clear. Close questioning brought out the fact that the patient had had puffiness of the eyelids during the first few days of the illness. Search of the blood and spinal fluid 34 days after the onset of symptoms failed to reveal any larvae. Biopsy performed the next day was positive. The patient was discharged on the twenty-second hospital day after considerable improvement. The combination of encephalitis and myocarditis is not extremely rare<sup>29, 30, 42</sup>; but the prognosis is poor. This patient was seen eight months later. She had made a complete recovery except for slight residual weakness of the right arm and leg. The eosinophiles were only 3 per cent; i.e., within normal limits.

It is interesting to note that in practically all the misdiagnosed cases recorded above, there was one clue, which if heeded, would have suggested the correct diagnosis; i.e., a history of *puffy eyelids* in the patient or in a member of the immediate family, or an *edema of the eyelids* noted during the physical examination. Sometimes the history of puffy eyelids was not obtained until after the diagnosis had been made, but most often the physician paid no attention to that aspect of the history or attributed it to some other condition. I should like to suggest that in taking the history in all acute illnesses, specific inquiry be made routinely concerning the presence of puffy eyelids; and if there is such a history or observation on examination, that the diagnosis of trichiniasis be seriously considered.

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## DIFFUSE PRIMARY TUBERCULOUS ENTEROCOLITIS; A REPORT OF TWO CASES \*

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DIFFUSE ulcerative tuberculosis of the intestines not associated with pulmonary tuberculosis is extremely rare, particularly in the United States. The subject is inadequately treated or completely ignored in most American textbooks and systems of medicine. For these reasons it was deemed advisable to report our experience with two cases, unique because of the extent of intestinal involvement and complete roentgenologic data. A review of the literature is included.

### REVIEW OF THE LITERATURE

In 1902 Heller <sup>1</sup> stated that the primary focus of the infection was intestinal in 30.6 per cent of tuberculous children. Edens <sup>2</sup> reported in 1905 that the initial focus was "abdominal" in 25 of 176 patients with tuberculosis. Beitzke <sup>3</sup> found 13 cases of primary intestinal involvement in 1100 autopsies. Eight of these were children and five were adults. In 1908 Fischer <sup>4</sup> reported three cases of what he considered primary bowel tuberculosis in adults. Hamburg, <sup>5</sup> on the other hand, failed to find a single instance of that type in 335 necropsies on children with tuberculosis. These older reports are difficult to evaluate because the pathologic nature of the primary complex was not fully understood prior to the studies of Ghon and of Ranke. Infection was frequently referred to as "abdominal" in origin with no attempt to segregate cases with ulcerative lesions in the bowel from those with only mesenteric gland disease.

Among other studies that may be quoted are those of Wollstein, <sup>6</sup> who reported six instances of tuberculosis of undoubted intestinal origin in 185 autopsies on tuberculous children. Later, with Spence, <sup>7</sup> she noted an incidence of 4.8 per cent of "primary abdominal involvement in 184 cases of childhood tuberculosis." Canti <sup>8</sup> stated that of 16 children with Koch infection, one had primary ulcers in the ileum. Opie <sup>9</sup> discovered no instance of healed mesenteric gland tuberculosis in 93 children and 50 adults living in St. Louis but did find such a condition in 18 of 66 British soldiers. Schurmann <sup>10</sup> reported that in 784 cases with a single primary complex in the lymph glands, this was abdominal in 102 or 13 per cent. Siegmund <sup>11</sup> stated that tuberculosis originated in the bowel in 3 to 4 per cent of all those infected. Scott <sup>12</sup> found 32 (10.6 per cent) primary abdominal infections

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among 300 Chinese dying of the disease. Blacklock<sup>13</sup> made a survey of 1800 consecutive autopsies on Glasgow children and found 283 to be tuberculous, the original focus being abdominal in 101 or 35.7 per cent of these. Iizuka<sup>14</sup> found evidence of a primary bowel lesion in 101 or 4.4 per cent of 2500 cases of Koch's disease. Maxwell<sup>15</sup> reviewed the autopsy findings of 233 cases of intestinal tuberculosis and reported 181 to be of the ulcerative type, among them being 15 cases (nine in children and six in adults) which were apparently "primary." Comessatti<sup>16</sup> found that in 159 instances of intestinal tuberculosis all but five were associated with pulmonary infection. The studies of Opie<sup>9</sup> and of Blacklock<sup>13</sup> as well as the earlier findings of Still (quoted by Wollstein<sup>6</sup>) call attention to the relatively high incidence of primary abdominal tuberculosis in the British Isles.

It should be noted that these reports were based upon necropsy findings in which the presence of characteristic changes in the mesenteric lymph glands was looked upon as evidence of the onset of the tuberculous infection in the bowel and that actual intestinal ulceration was found in only a few of the cases cited. Thus, of the 25 cases reported by Edens<sup>2</sup> only five revealed disease of the bowel wall itself at the time of death. Intestinal ulceration was encountered in only three of the 13 instances of primary intestinal tuberculosis described by Beitzke.<sup>3</sup> Fifty-seven of the 102 patients studied by Schurmann<sup>10</sup> had only mesenteric gland involvement. Intestinal ulcers were seen by Scott<sup>12</sup> in only three of his patients, who ranged in age from 10 months to 7 years. Blacklock<sup>13</sup> noted that in only 18 cases in his series was there naked-eye evidence of bowel ulceration—all of these being in children under five years of age. Even when ulceration was present, it was usually not very striking and involved only a relatively small area of the intestine. Iizuka<sup>14</sup> expressed the opinion that the visceral component of a primary intestinal lesion, that is, the bowel ulceration, has such marked tendency to prompt healing that it may be difficult to find macroscopically. In this connection, the work of Medlar and Sasano<sup>17</sup> may also be cited. They inoculated eight guinea pigs subcutaneously with tubercle bacilli. Serial sections of the lymphoid tissue in the bowel demonstrated tuberculous lesions and organisms in every case; yet only one showed a typically tuberculous bowel ulcer. The initial intestinal lesion seemed to occur in those intestinal glands which dipped deeper into the lymphoid tissue. From this point lesions were set up in the adjacent submucosa. The overlying mucosa might slough off and leave an ulcer but in many instances it remained intact, so that grossly discernible lesions did not occur in the bowel. The mesenteric lymph nodes were invariably infected. Such observations indicate that an initial lesion in the bowel wall may not be accompanied by obvious ulceration. Most workers are agreed that if the mesenteric nodes show evidence of primary tuberculosis, the original lesion occurred in the intestinal wall. The intestinal lesion may be easily overlooked, as Ferris<sup>18</sup> has demonstrated.

In addition to the statistical studies mentioned above, the literature contains reports of isolated cases of primary intestinal tuberculosis of the ulcera-

tive type. One of the most important of these is that of Reichle,<sup>19</sup> who reported an apparently primary tuberculous infection of a small segment of the distal ileum with caseous necrosis of adjacent lymph nodes in a boy eight years of age. In the same paper he included a brief description of an additional patient who may have had a primary intestinal complex. Pitts<sup>20</sup> reported the cases of two children of 11 and 2 years of age. The first had a few small tubercles in the lower jejunum with involvement of the mesenteric glands. The second had a tuberculous ulcer of the jejunum and caseation of the abdominal lymph nodes. In neither case was any additional focus of the infection discovered outside of the abdomen. Single cases of more extensive and apparently primary ulcerative intestinal tuberculosis have been recorded by Dixon and Beaver<sup>21</sup> and by Mourier.<sup>22</sup> The former presented the clinical and autopsy findings in a woman, 21 years of age, in whom the disease process involved the terminal 30 cm. of the ileum as well as the cecum and 12 cm. of the ascending colon. The latter reported finding very striking ulceration in the ileum, cecum and descending colon of a girl 17 years of age. In neither of these were roentgen-ray studies carried out during life. Schapiro<sup>23</sup> described the case of a man of 30 years of age with an extensive stenotic lesion of the mid-portion of the small bowel, which was resected with good results. The resected portion of the bowel and its adjacent lymph nodes showed changes highly suggestive of tuberculosis but acid-fast organisms were not found. Riche, Lonjon and Joyeux<sup>24</sup> also reported as an example of primary intestinal tuberculosis a patient with multiple stenotic areas in the ileum and infiltration of the cecum. The published description, however, leaves some doubt as to the exact etiology of the changes found and this may have been another instance of non-specific ileitis.

On the basis of roentgen findings, Pigorini<sup>25</sup> diagnosed primary tuberculosis of the upper small bowel in a patient 38 years of age. His report, however, contains no substantiating bacteriologic or pathologic studies. Colombo<sup>26</sup> reported the case of a man of 39 years of age, who showed roentgenographically a jejunal deformity and what seemed to be the result of pressure of a mass on the stomach and on the colon. Operation revealed an infiltrating lesion of the jejunum and a diagnosis of tuberculosis was made because of the gross appearance of the lesion. Neither biopsy nor bacteriologic studies were performed.

Investigations undertaken to determine the strain of tubercle bacillus responsible for primary intestinal tuberculosis indicate a preponderance of infection by the bovine type. This was true of 70 per cent of the patients studied by Siegmund<sup>11</sup> and of 9 of the 11 cases in Blacklock's series in which bacteriologic work was done. Mourier<sup>22</sup> found this variety of organism in the case reported by him and it was probably present in Reichle's<sup>19</sup> patient. This frequent isolation of the bovine strain is looked upon as evidence that the disease is often contracted by ingestion of raw milk from infected cows—a condition thought to exist more widely in England and Scot-

land than in this country. Giovanardi,<sup>27</sup> however, was able to produce intestinal tuberculosis in rabbits by feeding both the human and bovine strains of bacilli.

#### CASE REPORTS

This report is concerned with a description of 2 cases of extensive primary enterocolic tuberculosis.

*Case 1.* M. L., a 15 year old Slavish boy, born in Philadelphia, was admitted to the Graduate Hospital, June 24, 1935, complaining of severe abdominal pain, diarrhea, fever and weakness. His father gave a history of childhood tuberculosis. The boy had been admitted to a neighboring hospital in 1929 and again in 1930 and was stated to have had either recurring acute appendicitis or, possibly, abdominal lymphadenitis. No gastrointestinal examinations were made at that time. It was learned that since 1929 the boy had complained of bouts of slight abdominal discomfort at very infrequent intervals. In April 1935, two months prior to admission, moderately severe crampy pains developed. They were usually postprandial and not definitely localized. They gradually increased in severity and frequency and were associated with marked borborygmi and the development of sausage-like masses which the patient could palpate. Diarrhea began three weeks before admission, and the boy averaged eight watery stools daily during this time. Defecation did not relieve the pain. Blood, mucus and pus were not noted in the stools. Fifteen pounds were lost after the onset of these symptoms. There were no pulmonary symptoms.

On admission the patient was pale and emaciated. He appeared toxic and had a moderate afternoon fever. The chest examination was negative. The abdomen was moderately distended, but there was no evidence of ascites. At least three distinct sausage-shaped, tender abdominal masses were palpated. They were located in the upper left quadrant, lower midepigastrium and lower right quadrant. Other less prominent bowel segments were also felt. The ability to feel these tumors subsequently depended on the state of distention of the abdomen and the degree of tenderness and muscle guarding. They gave the impression of thickened, inflamed bowel segments. Rectal examination suggested some thickening of the rectal wall in the region of the first Houston valve. Proctosigmoidoscopy tended to rule out ordinary ulcerative colitis since there was no evidence of a diffuse inflammatory process of the mucosa. There was, however, an irregular granulating ulcerative area of inflammation, 3.5 centimeters in its transverse diameter and 1.5 centimeters longitudinally, on the right anterior wall of the rectum above the first Houston valve. This had overhanging edges and resembled an amebic ulcer. Scrapings and smears from these areas yielded no acid-fast organisms or amebae.

Tubercle bacilli were not recovered from the urine. The erythrocyte count was 2,900,000 with 7.5 grams per cent of hemoglobin and 6,300 leukocytes with a normal differential and no increase in young granulocytes. The Wassermann reaction was negative. Repeated examinations of the feces failed to demonstrate amebae. Dysentery and typhoid organisms could not be recovered by culture. Large numbers of the tubercle bacilli were found in six of the seven stools which were examined. A guinea pig, inoculated with a fecal emulsion, developed tubercles in the liver and spleen. The tubercle bacilli studied by Dr. Fred Boerner were believed to be the human strain. The tuberculin test was negative with precipitated tuberculin. The sedimentation rate was 54. The blood chemistry was normal except for moderate hypoproteinemia. Many of the stools were positive for occult blood.

Roentgenological examination was of great interest. The chest was examined twice and showed no evidence of parenchymal disease (figure 1). A preliminary plain film of the abdomen showed several very small calcified lymph nodes in the upper abdomen on both sides. Barium enema revealed an appearance of the colon characteristic of advanced ulcerative colitis with involvement from the cecum to the



FIG. 1. (Case 1) The chest is negative for pulmonary tuberculosis.

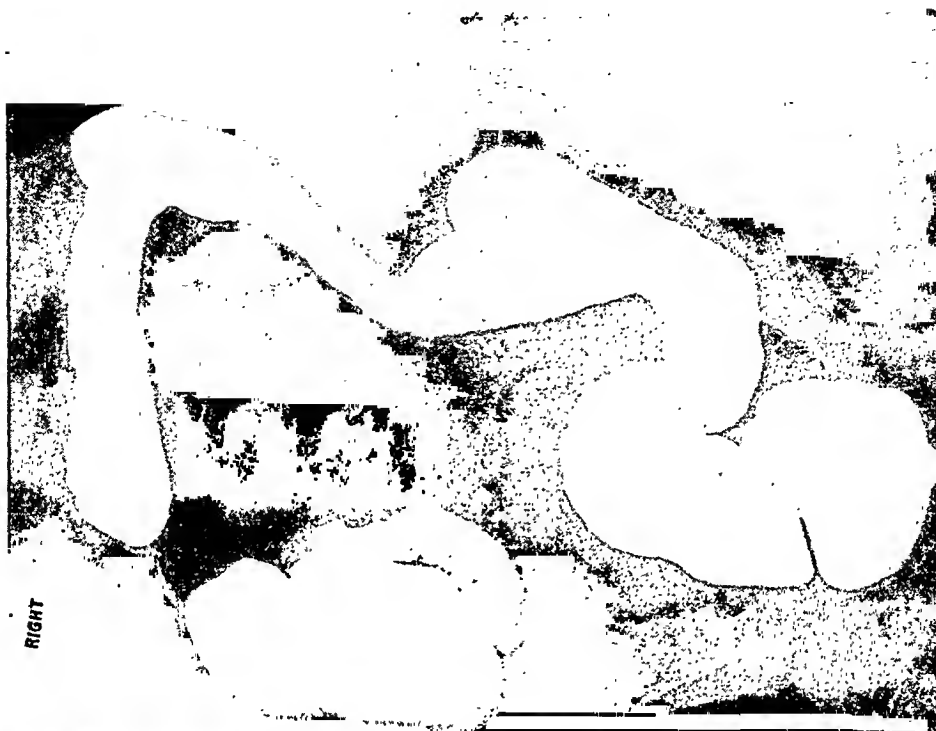


FIG. 2A. (Case 1) Barium enema study of the colon presenting the characteristics of an extensive and fulminating colitis. Before evacuation.



FIG. 2C. Double contrast enema. Note the disturbance in the mucosal pattern.



FIG. 2B. After evacuation.

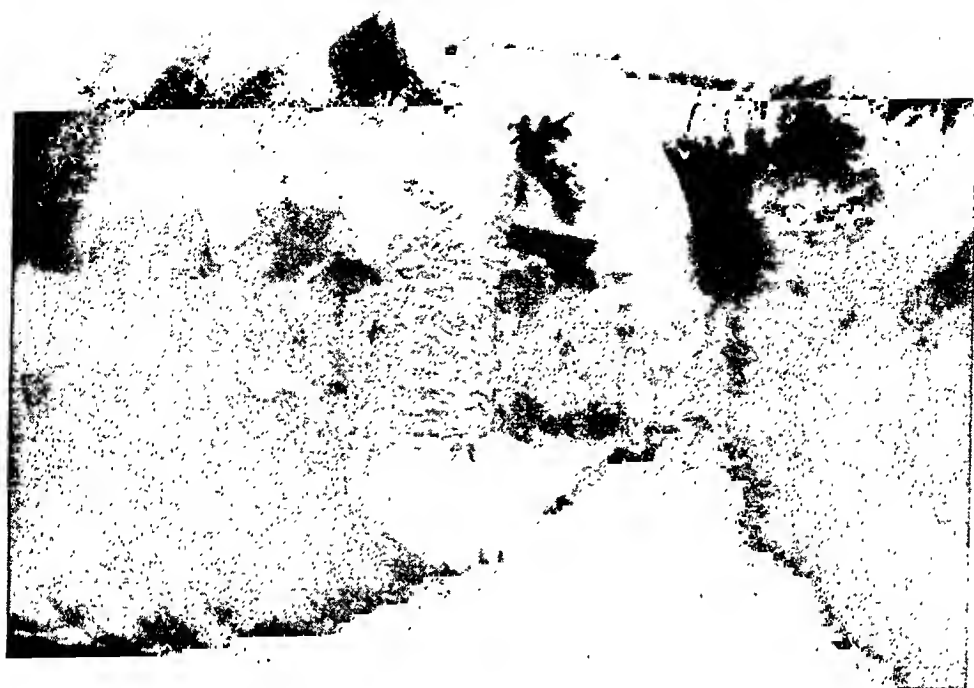


FIG. 3B. Taken one hour after figure 3A.

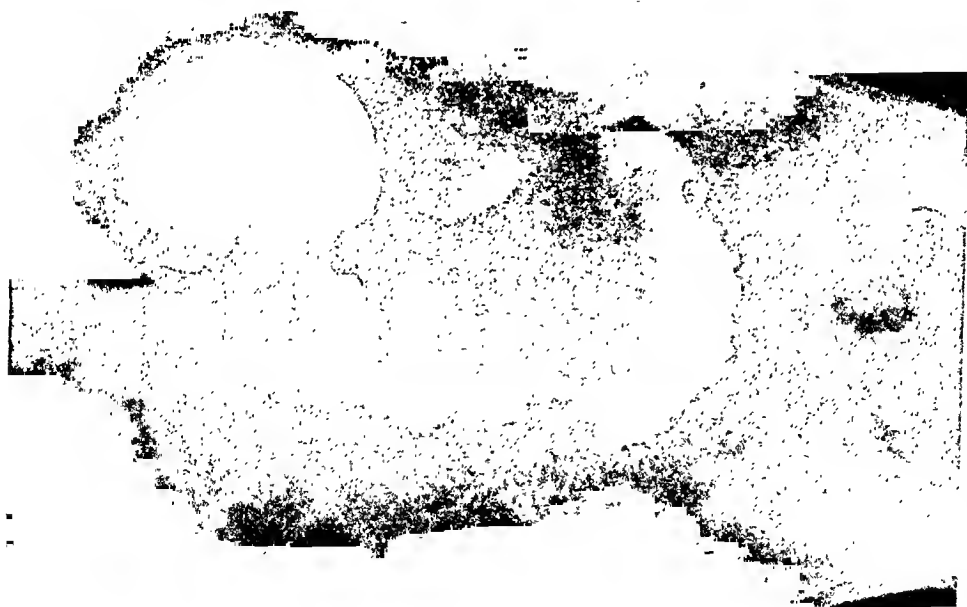


FIG. 3A. (Case 1) Primary tuberculous enterocolitis. Stomach, duodenum and proximal jejunum.

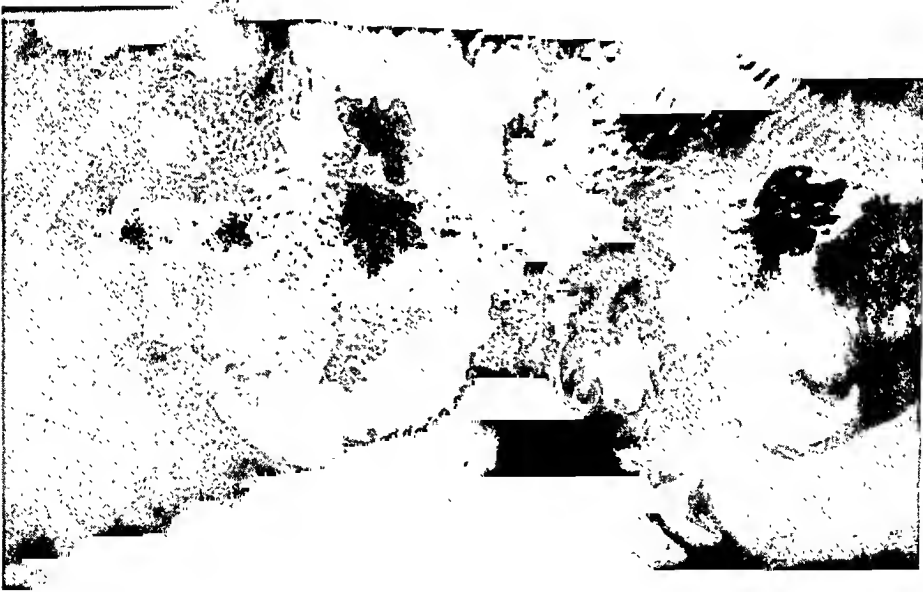


FIG. 3C. Taken two hours after figure 3A; extensive changes in the small intestine.

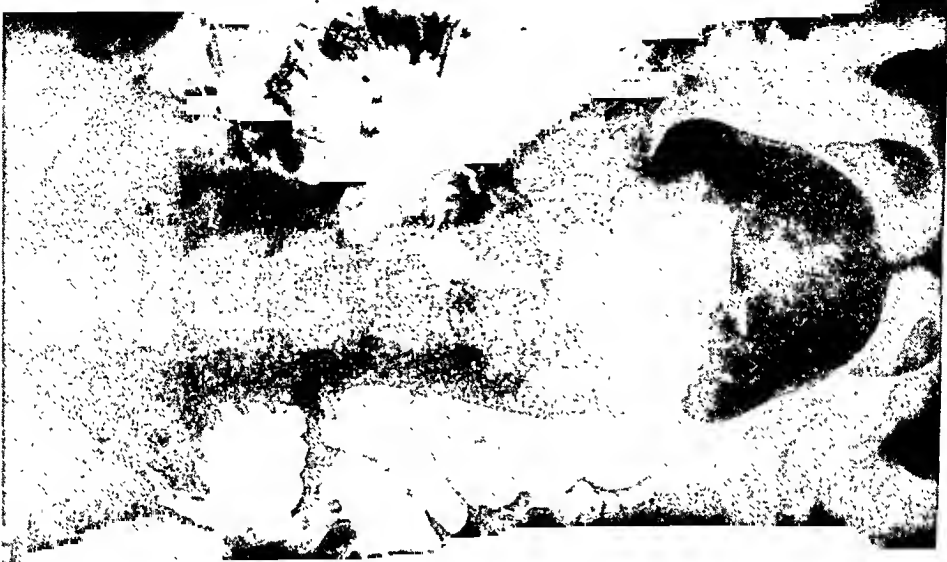


FIG. 3D. At six hours the meal has not yet reached the cecum.

sigmoid. There was considerable spasticity and irritability with shortening and narrowing of the colon and a lack of haustral markings. In addition, the silhouette of the colonic borders had a serrated, fuzzy appearance which we have frequently seen in the more acute fulminating types of colitis. The contents rushed into the loop of terminal ileum and showed definite dilatation of this portion of the small intestine (figures 2, 2B and 2E).

In the study of the upper gastrointestinal tract (figure 3) evidence of pathology became apparent as soon as the duodenum was reached. The duodenum distal to the cap was considerably dilated and showed an exaggeration of the mucosal rugae. This was found subsequently to be characteristic of the entire small intestine, the alteration being, however, definitely more marked in the jejunum and upper ileum. Some of the dilated loops were larger than a normal colon (figure 3B). While there were a few points of narrowing, dilatation of the bowel dominated the picture. The serrated appearance of the mucosal folds was a striking feature (figure 3C). Where this was absent the bowel wall presented a somewhat rigid appearance in spite of the dilated condition. The gastric motility was increased, while small intestinal motility was definitely delayed (figure 3D). Small patchy areas of the small bowel showed hyperperistalsis but in the dilated loops there was a definite stasis. The impression was obtained that the jejunum and upper ileum were more involved than the lower ileum. After reaching the colon, the opaque meal passed rapidly along into the descending colon (figure 3E). The appearance of the colon was essentially the same as found by barium enema examination.

Treatment consisted of a smooth, high caloric, vitamin rich diet, vitamin concentrates, calcium, iron, kaolin, ultraviolet radiation and transfusions. The course was rapidly down-grade. Abdominal pain became continuous and opiates were frequently necessary. The average afternoon temperature was 102°. Repeated examinations of the chest were negative. Symptoms of small bowel obstruction became more obvious. Exploratory operation, performed by Dr. Walter E. Lee, July 20, 1936, showed extensive tuberculous involvement of the entire jejunum and ileum and of the colon down to the sigmoid. The serosa of the entire bowel was studded with tiny tubercles. There were many areas of narrowing throughout the small intestine with dilated segments of bowel between. The parietal peritoneum, liver and spleen were not involved. The mesenteric glands were extensively enlarged and some seemed caseous. Biopsy of one of these showed typical tuberculous changes. Involvement was so extensive that resection or short circuiting could not be attempted. For a few days after operation the clinical situation seemed a little brighter, but a progressively fulminating toxemia developed. Death occurred August 4, 1936.

*Autopsy* by Dr. Eugene Case revealed a diffuse ulcerative tuberculosis of the large and small intestines. The ascending, transverse and descending portions of the colon showed enormous tuberculous ulcers and very little normal mucosa remained. The walls of the colon were very thick and tubercles protruded through to the serosa. The large bowel was adherent to the spleen and to several loops of small intestine. The proximal two feet of ileum showed the most marked changes in the small intestine. Below this level the ulcers were fewer and more discrete. The distal portion of the ileum showed no mucosal lesions. Many ulcers higher up in the bowel were healed. Miliary tubercles studded the serosa of the small intestines. All of the mesenteric lymph nodes were large and caseous. Miliary tubercles were found in the liver, spleen, kidneys and lungs. There was no primary tuberculous focus in the lungs.

## DISCUSSION

It is probable that bowel or mesenteric gland tuberculosis accounted for this boy's admission to a neighboring hospital five and six years before he



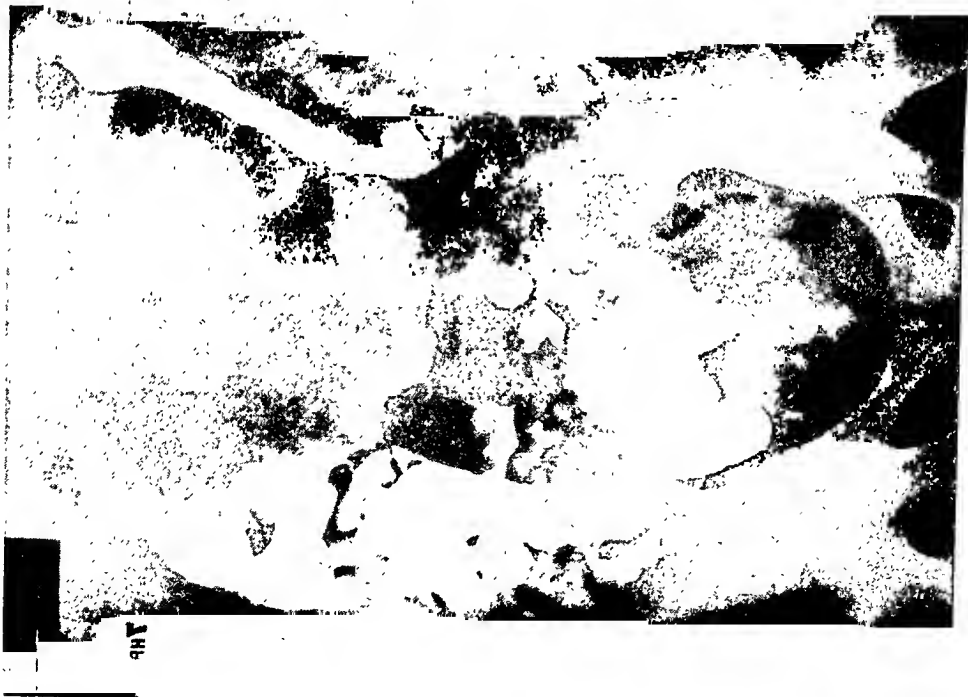


FIG. 3E. At seven hours the involvement of the colon is clearly shown.



FIG. 4. (Case 2) Repeated examinations of the chest were negative for tuberculosis.

was seen by us. There had been very occasional bouts of slight abdominal discomfort since the original attack. The necropsy revealed no evidence of previous appendiceal disease to account for these acute episodes. It is unfortunate that comprehensive studies were not performed at that time, as the disease may have been arrested had intensive therapy been applied. There is every reason to believe that the clinical manifestations of intestinal tuberculosis may be slight and infrequent for months or years and that involvement may be very widespread and of long duration, as it was in this case, before a critical picture is presented. It was obvious at the time of operation that the disease was old and far advanced and that it involved both the intestinal tract and the lymph glands. There was no evidence of miliary tuberculosis at that time. The rapid down-grade course following operation suggested a hematogenous dissemination of the infection by the manipulation which surgery entailed. In this instance the outcome could not have been altered but it is undoubtedly unwise to subject cases with this wide-spread involvement to laparotomy except for the relief of complete obstruction.

The extensive involvement of the colon is most unusual. The lesions were larger and seemed older than those in the small bowel. It is likewise of interest that the terminal ileum was entirely free from ulceration. The roentgenologist had remarked upon the comparative freedom of this part of the bowel from evidence of advanced pathology. The terminal ileum, so rich in lymphatics, is ordinarily the first part of the small intestine to be attacked in intestinal tuberculosis secondary to pulmonary disease.

*Case 2.* Less than five months following the admission of the first patient, on November 6, 1935, a Jewish boy, J. C., 14 years of age, was admitted to the Graduate Hospital, complaining of slight diarrhea, loss of weight and strength, and malaise. He was born in and always had lived in Philadelphia. We were unable to elicit a history of tuberculosis in the family. The past medical history was of little consequence. It included measles, pertussis, chicken pox, mumps and diphtheria. The initial symptoms of anorexia and weight loss began in September 1934, about 14 months prior to admission. About two months later a tendency toward diarrhea was noted. He passed from four to five soft stools daily. In December 1934, blood-tinged mucus was noted very infrequently in the feces. This situation remained unchanged until March 1935, when the patient was admitted to a neighboring hospital for study. He had lost 15 pounds in weight. After six weeks in the hospital (until May 15, 1935) he gained 10 pounds and the diarrhea disappeared. He was then admitted to a suburban convalescent home in July, where he remained for one month, gaining 10 pounds and becoming symptom-free. The same symptoms recurred in September 1935 and persisted until the time of admission. His general appearance suggested an approximate age of 11 years. There were no indications of adolescence. His nutrition was poor, and he weighed only 75 pounds. There was no edema or ascites. Abdominal examination revealed slight enlargement of both the liver and spleen. The temperature, although usually within normal range, mounted to 101° on several occasions. The erythrocyte count was 3,450,000, the hemoglobin 55 per cent, the leukocytes 7,700 with 60 per cent neutrophils, 34 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophiles. The nuclear index was 9.0 and the neutrophils showed some toxic granules. The sedimentation rate was 17 mm. Ag-

glutination tests with all available dysentery strains (Strong, Flexner and Shiga) were negative. The tuberculin test was negative. The only significant change in the blood chemistry was the hypoproteinemia, which the following figures show:

Date	Total Protein	Albumin	Globulin
11/13/35	4.86	3.0	1.86
11/18/35	5.15	3.0	2.15
11/23/35	5.2	2.8	2.40
12/2/35	8.2	3.9	4.3

Twelve stools were examined between November 7 and November 18. Gross blood or mucus was rarely present. The reaction for occult blood was positive only occasionally. Some specimens contained an excessive amount of fatty acid. There were no amebae or other parasites at any time. An acid-fast bacillus, subsequently shown by Dr. Fred Boerner to be a human strain of the tubercle bacillus, was found in three stools passed on different days. Sigmoidoscopy revealed several areas of mucosal hyperplasia surrounding rather small oval ulcerations in the region of the first valve of Houston. The mucosa traumatized easily in this area. The appearance was suggestive of healing anebic ulcerations but it was not quite typical of this. Scrapings from this area failed to show amebae or tubercle bacilli. Cultures from the bowel revealed only strains of colon bacilli. Because of the marked distortion subsequently found in the mucosal pattern of the stomach, somewhat suggestive of a hypertrophic gastritis, a gastroscopy was carried out. The mucosa was stated to be normal. A stained preparation of gastric sediment showed no acid-fast organisms and an inoculation of the sediment into a guinea pig did not induce tuberculosis. Free hydrochloric acid was present in the fasting residuum.

Roentgenological study was of great interest. There was no evidence of disease of the lung parenchyma, although the markings in the hilar regions were somewhat accentuated (figure 4). The stomach films suggested the presence of a hypertrophic gastritis. The duodenal cap was quite large but was never completely filled due to a pressure defect. In the light of the subsequent findings, this was thought to be due to pressure from a mass or enlarged lymph glands. The most striking feature of this part of the examination was the appearance of the small intestine (figure 5). The entire upper small intestine from the upper jejunum for a distance of six or eight feet showed a marked reduction in the size of the lumen (figure 5B). These loops arranged themselves in concentric parallel rings in the left abdomen (figure 5C). The walls of the involved portions of the small bowel appeared rigid and had a serrated contour. The mucosal pattern presented a mosaic appearance. There were various points of constriction throughout the diseased portion of the bowel. The motility of the opaque meal through the small intestine was not markedly disturbed (figure 5D). The cecum was never satisfactorily filled, appearing quite irritable and presenting a ragged outline. At six hours the meal had reached the splenic flexure but a considerable amount remained puddled in the terminal ileum, which was moderately dilated.

The barium enema study (figure 6) in this patient showed less involvement than was found in Case 1. The descending colon showed evidence of considerable irritability, if not rigidity, while the cecum was constricted and spastic. Difficulty was encountered in filling the cecum and none of the contents could be made to enter the terminal ileum.

The findings included a history suggestive of an organic bowel disorder, delay in physical development, fever, malaise, weight loss, palpable enlargement of the liver and spleen, anemia, hypoproteinemia, slight steatorrhea, sigmoidoscopic evidence of a circumscribed ulcerative process at the rectosigmoid, roentgen evidence of extensive disease of the small and possibly of the large bowel and, finally, the recovery



FIG. 5A. (Case 2) Primary tuberculous enterocolitis. Thirty minutes after ingestion of the opaque meal.

FIG. 5B. At two hours marked changes in the small intestine are noted.

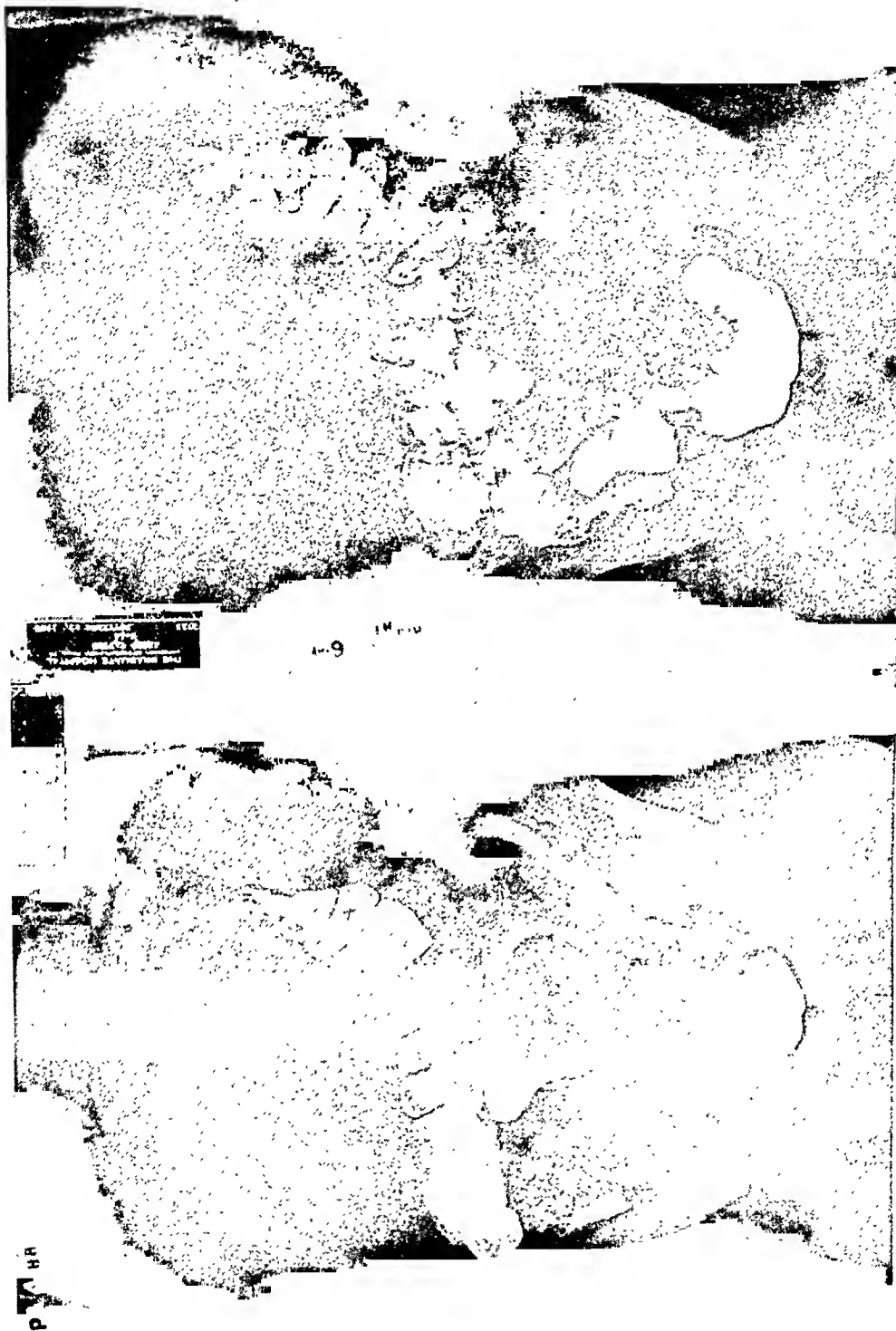


Fig. 5C. At four hours the small bowel involvement is clearly shown.

Fig. 5D. At six hours the meal has reached the splenic flexure. The ileum shows less involvement than the jejunum.

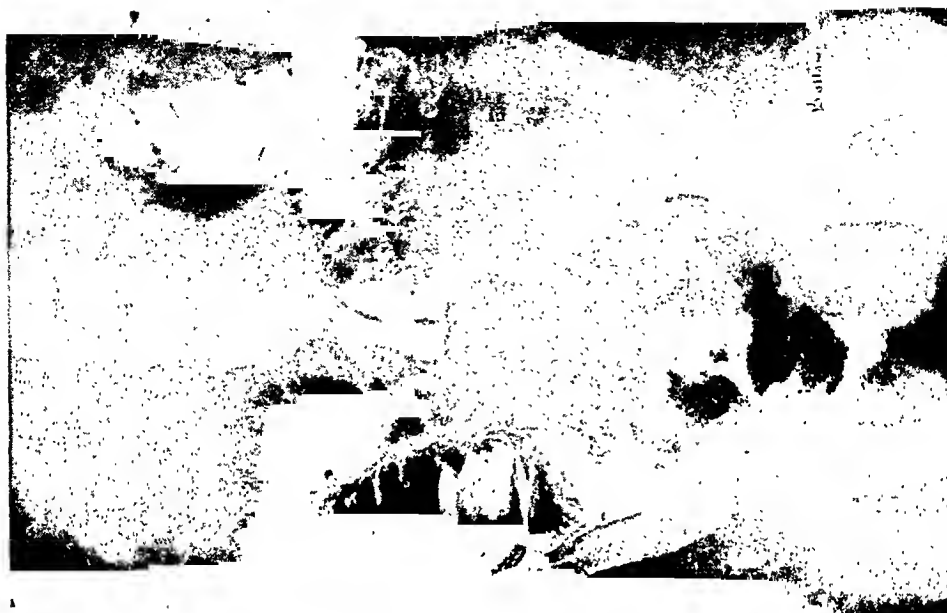


FIG. 6B. The colon after evacuation and inflation with air.



FIG. 6A. (Case 2) Barium enema study of the colon showing considerable irritability and spasticity.

of the tubercle bacillus in the stools. Because of our previous experience with Case 1 we concluded that we were dealing with a primary enterocolic tuberculosis. Treatment included a highly nutritious diet, ultraviolet radiation, vitamins C, B complex, A and D. Symptomatic improvement was rather rapid: the temperature returned to normal; the diarrhea abated and the blood count improved. The patient was sent to a convalescent home December 10, 1935.

After one month in the convalescent home he was readmitted to the Graduate Hospital for reexamination. He was then symptom-free but not up to standard weight and strength. Several hyperplastic granular areas were seen in the rectosigmoid on examination through the sigmoidoscope. Although several stools were examined at this time tubercle bacilli were not found. The blood count was normal except for persistent lowering of the hemoglobin. There was no appreciable change in size or consistency of the spleen and liver. The roentgen findings remained the same. The patient seemed in remarkably good condition considering the extensive bowel disease. Follow-up in the Out-Patient Department was uneventful until August 1936, when the stools again became mushy and occasionally blood-streaked and anorexia developed. Admission to the house for study in September revealed no change in the clinical status. The hypochromic anemia was noted again (hgb. 8 gm.). Roentgen findings were similar except for more dilatation of the upper jejunal loops (figure 7A). Roentgenologically it was thought that there had been definite progression of the disease in the small intestine but improvement in the colon. It was now possible to visualize the cecum. More intensive treatment and bed rest caused a remission in symptoms until early in December 1936 when a recurrence of mushy stools, anorexia, weight loss, malaise and anemia (hgb. 8.5 gm.) developed. Readmission on December 12 showed no essential changes in the sigmoidoscopic, physical or roentgen findings. Studies of the blood chemistry again revealed hypoproteinemia but were otherwise normal. Quick symptomatic improvement again followed bed rest and more regular medication and improvement in diet. Calcium, ultraviolet radiation and a high vitamin intake and iron were used throughout the illness. The patient had recurrences of symptoms in April and May of 1937 (figure 7B). These consisted of fatigue and exhaustion and slight diarrhea. He was readmitted to the hospital with each of these episodes and no essential changes were noted in his status except that a border-line positive result was obtained to the Congo Red test, suggesting the possibility of beginning amyloid disease.

The patient was seen regularly in the Out-Patient Department from May 1937 until August 1938. During this time he usually had only one or two fairly normal bowel movements each day and although anorexia was marked and he continued to be emaciated, he complained relatively little. He ate as much as possible of a high-caloric, high-vitamin diet and took vitamin concentrates and iron. The hypoproteinemia and hypochromic anemia persisted. Many stools were examined for acid-fast organisms but none was found. Roentgen-ray survey in January 1938 showed marked mucosal changes similar to those noted before (figure 7C). These changes were particularly marked in the proximal loops of the jejunum, which were seen to be markedly distended and also tubular and stiff. The cecum was well visualized. The chest showed no evidence of tuberculosis.

In August of 1938 it was necessary to re-admit the patient to the ward because of recurrence of diarrhea with seven or eight watery stools daily. The important physical findings at this time were extreme emaciation (the weight had dropped to 65 pounds), pallor, dehydration, slight pretibial edema, marked clubbing of fingers and toes and moderate hepatic enlargement. Another striking feature was the complete lack of sexual development. Sigmoidoscopic examination was performed a number of times during this stay in the hospital, but no definite mucosal disease was noted. A moderately severe hypochromic anemia necessitated continuous iron therapy and a number of transfusions. The plasma proteins ranged from 4.40 to 6.08 gm. per



FIG. 7A. (Case 2) Subsequent examinations show the variable but persistent nature of the small intestinal involvement. September 18, 1936.

FIG. 7B. May 26, 1937.





FIG. 7C. January 21, 1938.



FIG. 7D. September 14, 1938. All films in figure 7 were made approximately two hours after ingestion of opaque meal.

cent and the albumin from 2.39 to 3.45 gm. per cent. Transfusions and a high protein diet brought about no appreciable change in the proteins. Tubercle bacilli were not recovered from the stools and guinea pig inoculations failed to induce tuberculosis on this admission. The calcium and phosphorus levels in the blood were normal. A tuberculin test was negative. Roentgen studies showed no evidence of pulmonary tuberculosis. Examination of the epiphyses revealed slight retardation in development. No calcified lymph glands were seen in the abdomen. The changes in the gastrointestinal tract were similar to those previously demonstrated with stiffening and narrowing of the upper small bowel of perhaps a greater degree than at the previous study. The patient remained in the hospital for more than four months. During this time the diarrhea subsided and the blood count improved. There was no gain in weight, however, and on discharge his general condition was about as it had been prior to this most recent exacerbation of his illness.

### DISCUSSION

Four years have elapsed since the onset of symptoms and during the past three years this boy has been under our care, coöperating perfectly. He has not matured in any respect and remains extremely weak and on the borderline of complete invalidism in spite of being free of bowel symptoms a large part of the time. Aside from his failure to gain in strength and weight and his delayed puberty, it is remarkable that he is not more miserable with the extensive bowel disease. We have assumed that he has a well defined barrier in the lymphatic apparatus, preventing absorption, and accounting for the persistent anemia, hypoproteinemia and lack of physical development. It seems likely that there are few, if any, sizeable open ulcerations because the reaction for occult blood in the stools was negative usually and because of the failure to recover the tubercle bacilli since the first admission. The lesions at the rectosigmoid have healed completely.

### SUMMARY

The literature contains very few instances of primary ulcerative intestinal tuberculosis after the age of eight years. The ages of these boys were 15 and 14 years when admitted. However, the onset may have been at the age of 10 years in the first and at the age of 13 years in the second boy. It was not possible to trace the source of the infection in either case. The milk supply was assumably above suspicion, and there had been no contact with active pulmonary tuberculosis in the household. The bacteriologic studies of Dr. Fred Boerner indicated that the organisms in both cases were of the human strain. There was no evidence of pulmonary tuberculosis past or present in either patient, although M. L. died of miliary tuberculosis after exploration. Their clinical manifestations were dissimilar. M. L. was admitted in a very toxic state with many points of partial bowel obstruction. The second boy was not acutely ill and has developed no signs of obstruction after more than three years of observation. His clinical condition seems almost entirely the result of a nutritional deficiency state, characterized principally by anemia, hypoproteinemia and lack of growth

and development. We are dependent entirely upon the finding of the tubercle bacillus in the stools on the first admission for our clinical diagnosis. This type of case causes one to speculate concerning the possible tuberculous origin of other cases of extensive so-called non-specific enteritis. It is still a moot point whether tuberculous lesions of the bowel may not heal completely, leaving a stenosed bowel segment with blockage of lymphatics predisposing to secondary infection. It is possible that such cases may later masquerade as so-called regional enteritis, although it is most unlikely that many cases of chronic regional ileitis actually started as tuberculosis. It is of interest in this connection that many of the ulcers in the intestine of M. L. were found to be healed at necropsy and there is no reason for feeling that almost complete healing of open ulcers has not occurred in J. C. to account for our failure to recover acid-fast organisms since his first admission and the frequent absence of occult blood in his stools. The roentgen study reveals a bowel silhouette characteristic of the stenosing cicatrizing lesion of regional enteritis except for the extent of involvement.

We have not encountered in the literature a report of primary bowel tuberculosis with such widespread involvement. The distal duodenum, jejunum and upper ileum were completely involved, the terminal ileum being spared in the first case and the last segment to be involved in the second case. No previous report of involvement of the entire colon, such as that present in M. L. has been found in the literature of primary intestinal tuberculosis. In both cases lesions were seen at the rectosigmoid which were undoubtedly tuberculous, although we were unable to recover the organism through the sigmoidoscope.

We have practiced a careful search of many stools for the tubercle bacillus in all patients with ulcerative lesions of the small and large bowel. In cases presenting clinical features suggestive of tuberculosis, stools should be repeatedly examined as organisms may be absent from the stools for considerable periods and present in large numbers at other times. One other feature worthy of comment concerning the stool analysis is the interpretation to be placed upon steatorrhea. A diagnosis of idiopathic steatorrhea is fraught with danger and must never be made until a thorough roentgenologic and bacteriologic survey definitely excludes organic small bowel disease. Steatorrhea is an early and common accompaniment of many types of chronic enteritis, severe enough to disturb motility or intestinal absorption. Naturally it was present in both cases.

No adequate roentgenologic description of primary bowel tuberculosis appears in the literature and certainly there has been no record of cases showing this degree of involvement. Summarizing the roentgen findings in these cases it is seen that the changes occurred in both the large and small bowel. In the small intestine, the disease was characterized by areas of constriction and dilatation. While either of these may predominate it is obvious that constriction is the primary change with dilatation resulting secondarily. Irritability and spasticity of the small bowel seemed not to be

particularly conspicuous, which is in direct contrast to the findings in the colon. Of particular importance is the marked irregularity noted in the outline of the small intestine, indicating mucosal involvement. One case showed a distinct mosaic pattern of the intestinal mucosa. The effect of these changes upon small intestinal motility is variable. In well advanced cases such as here described the changes are quite striking and readily detected. The ordinary gastrointestinal study as customarily conducted would surely detect the condition but a true appreciation of the extent and degree of involvement could be obtained only by a careful and thorough progress-meal study of the small intestine. Such a study would most certainly be required in early cases of lesser involvement.

### CONCLUSION

Two cases of primary tuberculous enterocolitis are reported and the literature reviewed. In both cases the age of onset was later than most cases previously reported. The extent of involvement was noteworthy. A mixed nutritional deficiency state constituted the clinical picture in one and a typically toxic state, with bowel obstruction, the other. We wish particularly to record the roentgenologic features which we have not seen presented previously in cases with such extensive involvement. The disease is of interest at this time because of the recent literature which has been devoted to chronic non-specific enteritis and enterocolitis. Primary tuberculosis must be considered in all such cases occurring in early life when the involvement is extensive. The finding of tubercle bacilli in the stools repeatedly, in the absence of pulmonary tuberculosis, justifies a diagnosis of bowel tuberculosis.

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## CHEMICAL SPECIFICITY IN GROWTH AND DEVELOPMENT\*

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THERE is steadily increasing recognition of the fact that fundamental cancer research does not necessarily mean the study of cancer. That cancer is just one phase of the growth problem is so self-evident that it admits of no argument. The problem, indeed, was placed on the doorsteps of biologists in this form many years ago by many of the great pathologists. In adopting this point of view, when the staff of the Lankenau Hospital Research Institute was organized some twelve years ago, we were promptly confronted with the confusion in which the word "growth" was floundering, a confusion recognized by but a meager few and compensated by them by using suitable adjectives to describe the kind of growth which they were discussing. We first attempted to clarify our thoughts in this matter, and then to interject some chemistry into them. This entrance of chemistry into the field is natural and surely requires no comment. We present in this paper, then, one particular aspect of chemistry as applied to growth, leaving the implications of this work to cancer research to the reader.

In the approach to any problem common sense suggests that extraneous matters be brushed aside. This is as necessary in the field of growth as anywhere else. For here as elsewhere there is, as stated, loose thinking and looser nomenclature.

The word growth is used to designate anything from elongation of a root to increase in area of a tissue culture; from metamorphosis of a tadpole to increase in weight of a rat. Yet anybody who thinks knows that each of these activities is expression of a distinct and individual set of processes.<sup>1</sup>

The time has come to get down to fundamentals, and it will be necessary first to consider the source of a reaction rather than the signs thereof.

Now there are four principal aspects of living things, viz., direction, substance, state of substance, and form. These are respectively subserved by the basic sciences of genetics, chemistry, physics, and anatomy. Genetics is primary because it determines the direction of succession and persistence. Chemistry is next in importance because without substance and its reactions there could be no expression of direction. Physics is third for through the state of substance the extent and rate of living are determined. And anatomy is basic because through structure function is expressed.

The substance of living things is composed of chemical atoms combined

\* Read at the New Orleans meeting of the American College of Physicians, March 31, 1939.

From the Lankenau Hospital Research Institute, Philadelphia, Pa.

into molecules. The activities of living are expressions of reactions between these molecules and their groups.

Growth is an activity of living. The substance of growth is therefore composed of molecules and groups, and growth is an expression of reactions between these chemical molecules and groups.

But what is growth? Is it simple increment or is it the expression of the sum total of processes used to bring an organism from its beginning to the functionally mature state?

To our mind growth is not single—it is multiple—the summated expression of integrated developmental and incremental processes, participants, and determinants.<sup>2</sup>

In this there are five chief sets of activities. There are the processes concerned in the preparation of the field for emergence of new structure. These are comprised in the developmental activity of **initiation**. There are the processes concerned in cell increase in number. These are comprised in the developmental activity of **proliferation**. There are the processes concerned in cell specialization or chemical individuality. These are comprised in the developmental activity of **differentiation**. There are the processes concerned in cell segregation or cell conjunction into functionable units. These are comprised in the developmental activity of **organization**. And there are the processes concerned in the incorporation of living substance into that already present. And these are comprised in the developmental activity of mass increment or **anabolism**.

Under these five may be encompassed all that concerns growth.

Each set of activities is obviously separate in function. But growth is not accomplished by their isolated expression. It is accomplished by the successive dominance of these activities in coterminous expression. That is to say, all work together but each predominates at some stage or another in the growth progression.

Each set of activities is also separate in expression as it is in function. Therefore each must have its own set of chemical participants, determinants, and reactions. Herein lies the chemical specificity of growth and development.

The chemical and functional specificities of vitamins, exocrine, and endocrine products are known, or are rapidly being uncovered. But these are not of present interest since they are not only late additions to developmental phylogeny, but also more concerned in adaptation of individuals than in developmental activities of general expression.

Our interest lies in finding the chemical nature of the participants, determinants, and reactions specific to those growth activities which are the common possession of all living things; those which are essential to the bringing of every living thing to completion. Attention is on the chemical specificities of **initiation**, **proliferation**, **differentiation**, and **organization**. It is not on the chemical specificity of root elongation in plants or bone growth in animals.

It is logical for this purpose then, to look to compounds which are components of living things in general, and to brush aside those which are limited in their occurrence to the particular.

In their application to cancer, it need be remembered only that cancer may be stated in all truth to be a deviation of growth possible in all living things, at least in all multicellular organisms.

These naturally-occurring tissue constituents of general distribution are nothing other than the amino acids and the nucleic acid components.

Knowledge of the specific function of any one of these ubiquitous compounds has hitherto been lacking. This is strange, for surely the specific functions of the substances of living are primary; and secondary are their general properties of acting as structural units, as energy producing combustibles, and as contributors to the reaction basis of living.

Because each of these compounds is present wherever substance is living, and because each has its own individual and specific chemical make-up and attributes, the hypothesis was set up by Hammett that each must have its own distinctly individual and specific part to play in some one or other of the several basic growth activities essential to the bringing of an organism from its beginning to its functionable maturity.

As stated, for the past twelve years investigations along this line have been pursued at The Lankenau Hospital Research Institute and its Marine Experimental Station.

The results have unquestionably validated the hypothesis and established it as an experimentally substantiated concept. There can now be no question but that each and every amino acid and nucleic acid component has its own characteristic influence on growth and that this can be traced to the specific character of the chemical configuration involved.

For these experiments it was necessary that an organism be used in which the various phases of growth and development could be separated, one from the other. Significant also would be conditions of metabolism as factors in growth and development. Thus when new tissue is being laid down by proliferation of cells, anabolism is in the ascendancy. When differentiation is taking place within the protoplasm of the cells laid down by proliferation, chemical reconstitution is dominant; basic, more or less universal, compounds, groups and molecules are rearranged into specific and specialized kinds such as go into the make-up of epithelium, muscle, bone, nerve, or whatever tissue is being differentiated. When the completed animal is finished, neither anabolism nor catabolism is in the ascendancy. There is maintenance metabolism whereby analytic and synthetic processes are nicely balanced in that dynamic equilibrium which is called "life." When regression sets in, catabolic processes are in the ascendancy; larger and more specific molecules are broken down into simpler and more general molecules and groups.

As a beginning in this problem such an organism as the above necessities dictated was found in the marine hydroid *Obelia geniculata*. This is



a colonial-living animal attached by a stalk to a barnacle, shell, or convenient rock. From the main stalk grow side branches at the end of which completed organisms are developed. Two types can be recognized, one, the gonophore, producing medusae, and the other, the vegetative form, or the hydroid itself. On the stalk, or one of its branches, there appears a bud which increases in size by proliferation, anabolism being in the ascendancy. The bud continues proliferation and a cone-shaped end is developed. Inside of this cone-shaped structure differentiation occurs and then organization of the differentiated structure until the complete animal with its tentacles is the final result. After a time regression sets in; the tentacles slowly disappear and the protoplasm within the cup-shaped body undergoes disintegration, finally leaving an empty cup as the end result of its life cycle. During the differentiating stage there is chemical reconstitution to produce the complete organism. During its span as complete animal, metabolism is of the maintenance variety. During regression catabolic processes are in the ascendancy. During the course of these processes protoplasmic streaming occurs from the main stem predominantly outward into the bud. That is, during this period fresh building blocks are carried to the organism for its use in chemical addition and reconstitution. During the mature stage the stream is backward and forward; during the period of regression the stream is predominantly inward toward the main stalk. For convenience the stages of growth and development can be divided into one-fourth developed, one-half, three-fourths, complete, and senile.

Recording of the results of the experiments was dynamic. Records were made of the condition of organisms at the beginning of an experiment. They were then exposed to the effects of a number of chemical compounds for a given length of time. At subsequent examinations the stages reached by the various organisms were again recorded. As an example, if, in a given group 25 were in the half stage, and 25 in the three-fourths, record was made of the progress from the proliferation to the differentiation stage; and from the state of differentiation to that of organization to the complete functionable animal. Thus the effects of any given chemical compound on initiation or proliferation or differentiation or organization were recorded. Following is a list of compounds which have been tested, and a statement of results. For further details reference is made to original publications.

Glycine accelerates regeneration.

Alanine has no apparent effect on the growth of the animal other than that which can be attributed to its specific dynamic action.

Phenylalanine may, as a potential source of tyrosine, forward differentiation.

d-Glutamic acid hastens differentiation and organization.

Tryptophane retards catabolism and thus may indirectly stimulate general growth.

Histidine may act similarly through its sustaining effect on metabolic expenditure.

Uracil favors recurrent growth and retards differentiation, regeneration and metaplasia.

d-Arginine has an effect similar to that of Uracil, which suggests the latter as a natural precursor of the former.

d-Ribose has no specific effect on any of the developmental growth activities.

Allantoin might favor growth in general but it has no specific influence on increase in cell number.

dl-Methionine stimulates proliferation. Results are consistent with the assumption that methionine may be converted to cystine in the living organism.

l-Aspartic acid is specific for differentiation.

d-Lysine is essential to mass increment by participating in some intermediary process.

Thymine is significant in proliferation and differentiation.

Cytosine helps differentiation.

l-Hydroxyproline accelerates proliferation and differentiation.

l-Proline forwards differentiation and retards proliferation.

Adenine enhances organization and retards initiation.

Xanthine forwards regeneration.

Guanine forwards initiation and organization.

From these results there emerge a number of generalizations. But one will be mentioned.

The compounds which influence differentiation are d-glutamic acid, l-aspartic acid, l-proline, l-hydroxyproline, tyrosine, cytosine and thymine. These in common may yield a single type of chemical grouping, viz., the pyrrolidone configuration. Perhaps it is this simple chemical group which is found so freely and frequently in intermediate metabolism that is the chemical key for the unlocking of that chemical specialization of cells which is called differentiation.

The experiments to be done in relation to cancer are obvious. Anatomically, cancer cells do not differentiate normally and do not organize at all. Is it because the cells cannot by reason of a changed internal chemical make-up, or is it because the environment does not furnish the requisite building blocks? Offering to cancer cells, compounds with the pyrrolidone configuration actually or potentially present should help decide this long-asked question.

### SUMMARY

Fundamental cancer research does not necessarily mean that cancer itself is studied. Cancer is but one phase of the growth problem; therefore studies of growth in general have some bearing on cancer. The word "growth" is ambiguous and so should be modified by adjectives or phrases such as growth in size, growth in number, differential growth, developmental growth, etc., when discussed.

The entrance of chemistry into the growth problem is natural. The particular discussion of the paper, of which this is an abstract, is concerned with this question. Inside of cells are numbers of chemical molecules, groups and atoms. What do they do inside of cells in relation to growth and development? The amino acids and certain nuclear compounds have been studied and it is found that each one thus far tested has its own particular part to play in growth and development. There is then chemical specificity for the various phases of growth. The effect of these compounds

will be enumerated. A few problems will be set up from these results in direct relation to cancer.

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# CASE REPORTS

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## HYPERACTIVE CAROTID SINUS MECHANISM IN AURICULAR FLUTTER; A CASE REPORT\*

By N. HIATT and L. ADAMS, *Chicago, Illinois*

THE combination of auricular flutter and a carotid sinus sufficiently hyperactive to lead to syncopal attacks and convulsions has not hitherto been reported. Such a case was recently seen at the Michael Reese Hospital and because of its rarity is presented in this communication.

### CASE REPORT

The patient, a 66 year old white streetcar motorman, first entered Michael Reese Hospital in July 1936, because of hunger, thirst and polyuria, which had been gradually increasing during the preceding three years. One week before entrance to the hospital, the patient had fainted while driving his streetcar. The doctor consulted at this time discovered a four plus glycosuria and a blood sugar of 206 mg. per cent, and sent him into the hospital in order to control the diabetes.

The family history was not contributory. The fainting spell of a week before admission was identical with several he had had in the six months preceding. While maneuvering his streetcar from the barn in the morning, he would suddenly faint. After lying down for several minutes, he would arise feeling perfectly well and continue his day's work without interruption. In addition, for the past two or three years he had noticed that extreme dizziness would follow any attempt to look upward abruptly. In fact, this condition had become so extreme that the patient could not mount more than one rung of a ladder without falling. Finally a history of increasing exertional dyspnea for the past 15 years was elicited. At the time of admission a two-block walk made the patient short of breath. There was no associated pain, palpitation or other evidence of diminished cardiac reserve.

The pertinent physical findings discovered on this admission were: mouth edentulous; two small areas of leukoplakia on the right lower alveolar ridge; considerable angiosclerosis of the retinal vessels; the apex of the heart could be palpated just beyond the nipple line and the heart tones were distant; the contour of the chest was emphysematous and the peripheral vessels were sclerotic.

The blood pressure on admission was 156 mm. of mercury systolic and 70 diastolic. Wassermann and Kahn tests were negative, blood non-protein nitrogen was 32 mg. per cent and the sugar 220 mg. per cent. Except for four plus sugar, the urine was negative.

During this stay in the hospital, the temperature was always normal and the pulse always regular, varying between 60 and 80. The diabetes was rapidly controlled by means of diet and insulin, and the patient left the hospital in 10 days with no glycosuria and a blood sugar of 90 mg. per cent. After his discharge from the

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hospital, the patient was free from diabetic symptoms although he was prone to be careless with his diet and to take insulin irregularly.

A year and a half later, in January 1938, the patient returned to Mandel Clinic complaining of a painless, intermittent hematuria of a week's duration. He was put on a diabetic diet with small amounts of insulin and sent into the hospital. The fainting spells which accompanied his attempts to maneuver his streetcar from the barn in the morning had become so frequent that he had been retired from his job on a pension. Since stopping work, he had had no more fainting spells, although he still occasionally became dizzy when he looked up abruptly.

In addition to the previously noted positive physical findings, those on his second admission were: blood and blood clots in the second glass of urine, evidence of some weight loss and a moderately enlarged, non-tender, nodular prostate.

The blood pressure was 155 systolic and 80 diastolic, and the blood count and blood chemistry (including the blood sugar) were perfectly normal throughout the hospital stay.

Soon after admission the patient was cystoscoped and a tumor mass infiltrating the vertex and posterior wall of the bladder was discovered, biopsied and thoroughly fulgurated. The biopsy report was squamous carcinoma of the bladder. In 10 days the patient left the hospital with a clear urine.

During this stay in the hospital, the pulse was always between 70 and 90, and regular.

In March 1938, some six weeks after leaving the hospital for the second time, the patient returned to the Mandel Clinic with pain in his right lower jaw. Beneath his denture, on the right alveolar ridge, was discovered a raised, hard, granular area extending from the second bicuspid to the retromolar triangle. No associated lymph nodes were found, nor did roentgen-ray reveal any invasion of the mandible or metastases to the chest. The biopsy disclosed no definite evidence of carcinoma. The lesion was treated with radium and, after six weeks of treatment, disappeared.

In September of 1938, the patient was cystoscoped again and a small recurrent papillary tumor discovered at the trigone. Before the patient could be sent into the hospital, however, it was noted that he had a pulse rate of 152, which was perfectly regular. Consequently the patient was sent to the cardiac out-patient clinic before being admitted to the hospital. Here, in addition to the old history of exertional dyspnea, mild orthopnea and nocturnal cough for the past few months were reported. The only additional positive physical findings at this time were a very light pitting edema of the lower extremities and a slowing of the pulse on carotid sinus pressure. The blood pressure was 150 systolic and 90 diastolic, the pulse 150 and regular. A roentgen-ray plate showed heart enlargement (13.7/26.7 cm.), chiefly of the left ventricle. An electrocardiogram showed a left ventricular preponderance and an auricular flutter, with an auricular rate of 300, a ventricular rate of 150, and two to one conduction.

The patient reentered the hospital on the genito-urinary service in October 1938, for refulguration of his bladder tumor. The physical findings were essentially the same as those of the past two and a half years, except that on occasion a soft systolic blow was heard at the apex of the heart, and the liver was felt two fingers-breadth below the costal margin.

The urine contained many red blood cells but was otherwise negative. The blood count and blood chemistry (sugar and non-protein nitrogen) were within normal limits during his entire hospital stay. By means of diet and a small amount of protamine insulin (U 10) the patient's urine was kept sugar-free, and blood sugar was held around 100 mg. per cent. The blood pressure on admission was 140 systolic and 100 diastolic and thereafter varied between a maximum of 150 systolic and 100 diastolic postoperatively to a minimum of 140 systolic and 80 diastolic on discharge. The pulse on admission was 140 and regular. During the hospital stay, it was always regular and

generally ranged between 120 and 160. On several occasions, however, it fell to 80 or 90, although never for more than 10 to 20 minutes.

Soon after admission the patient's bladder tumor was again thoroughly fulgurated. The postoperative course was entirely uneventful, and after several days, when he was again completely comfortable, the patient was transferred to the medical service of Dr. L. Bloch because of the persistent tachycardia. It was now discovered that eyeball pressure slowed the pulse rate; also that momentary compression of the right carotid sinus when the patient was sitting up caused the ventricles to stop instantly and the patient to become unconscious almost immediately and have a convulsion soon after. Later the patient identified this episode with the fainting spells which had led to his retirement a year and a half before. Irritation of the carotid sinus by metastatic malignancy was suspected, in view of the fact that the patient had been treated only six months previously for a lesion of the mouth that was possibly a carcinoma. A careful search, however, revealed no demonstrable nodes in the neck, nor any evident lesions of the larynx, pharynx or pyriform sinuses.

Two weeks postoperatively the patient was discharged with a normal urine, and with his diabetes under control. No attempt was made to convert the flutter at this time, nor to denervate the carotid sinuses, because the patient became uncoöperative.

### DISCUSSION

During his stay in the hospital, several procedures were carried out which helped to illuminate the mechanism of his fainting attacks and convulsions. The patient was not coöperative at any time, because he was convinced that the tests were affecting his heart. He did not regard the unconsciousness incident to the pressure on the carotid sinus as unpleasant, but after the first few tests, refused to stand or sit up during carotid sinus stimulation. Consequently all of the electrocardiographic studies were done in the supine position.

A typical convulsive seizure, while the patient was standing or sitting, could be precipitated by pressing on the right carotid sinus for about a second. The sequence of events was uniform. Almost simultaneously with the application of the pressure the pulse disappeared, the patient began to sweat slightly, became extremely pale and lost consciousness. Generalized convulsive tremors appeared after about 15 seconds, accompanied by a right deviation of his head, exophthalmus and a coarse nystagmus to the right. At this time, the pulse could always be felt, beating slowly and irregularly. After about 20 seconds of convulsions, the patient regained consciousness, his face became flushed, the convulsive movements rapidly subsided, and the regular rapid pulse returned. The entire episode lasted about one minute. Subjectively, when the right carotid sinus was pressed, the patient felt faint, the sensation being identical with that experience during the fainting spells that he had had for the past two and a half years. Pressure on the left sinus caused an almost identical effect, including the turning of the head and nystagmus to the right.

With the patient supine, his head supported by one pillow, asystole and unconsciousness (which seemed to parallel each other) could readily be elicited by pressure on either sinus. Convulsive movements, however, occurred inconstantly, and then only with pressure of five seconds or more. Pressure over both sinuses for from one to three seconds while the patient was supine was as effective as pressure over either one when he was erect.

The studies in which the electrocardiogram was recorded were all done when the patient was supine. Analysis of the records showed an auricular flutter, with an auricular rate of 300 and a ventricular rate of 150.



FIG. 1. Effect of compression of the right carotid sinus for one second (Lead II). Arrows mark out time of compression.  
Note short period of ventricular asystole.

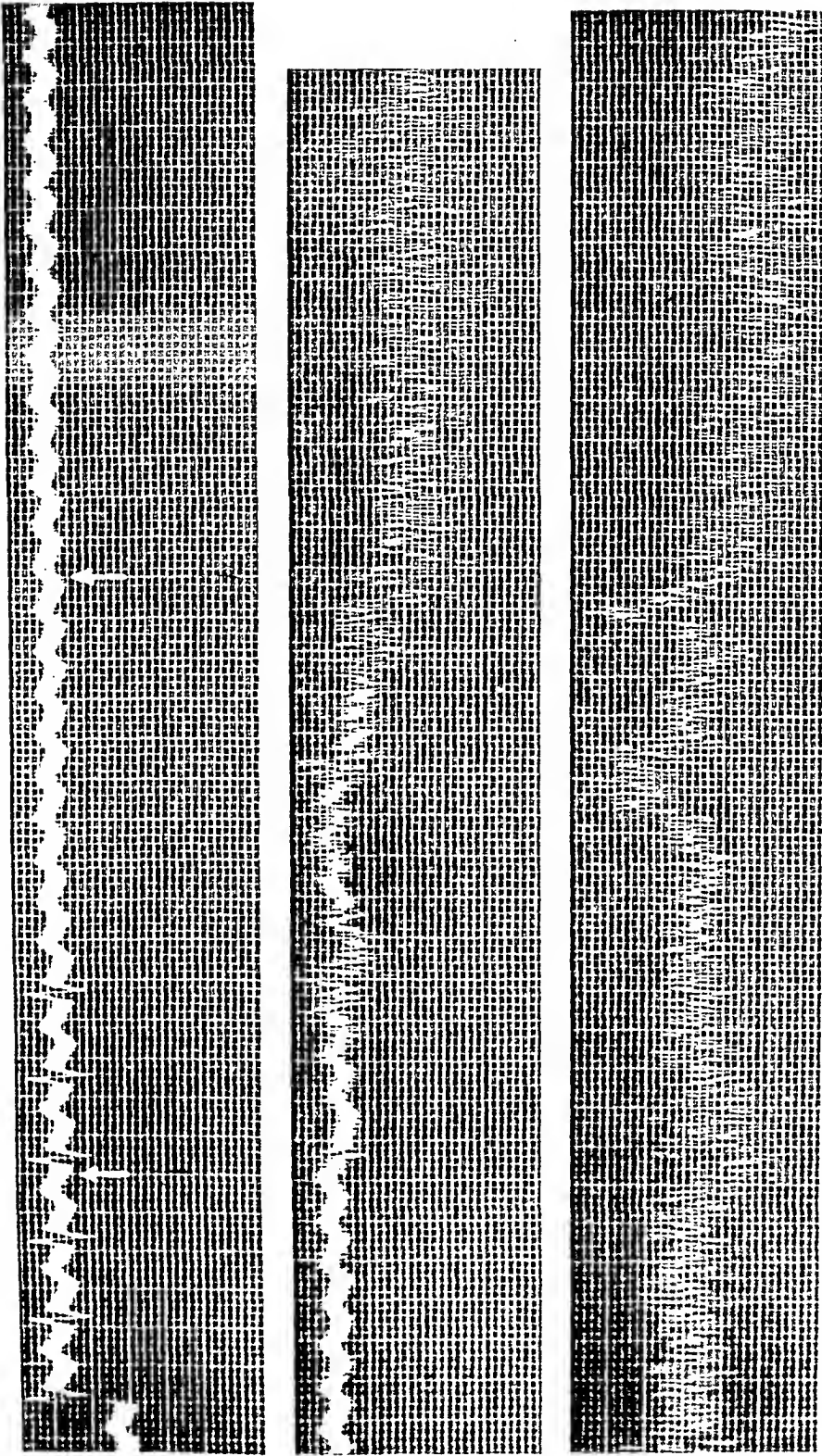


FIG. 2. Effect of compression of both carotid sinuses for three seconds (Lead II). Arrows mark out time of compression (a continuous record). Note long period of asystole and evidence of convulsions, the latter starting after the former and outlasting it. Also note the second period of convulsions without ventricular asystole or other evidence of circulatory disturbance.



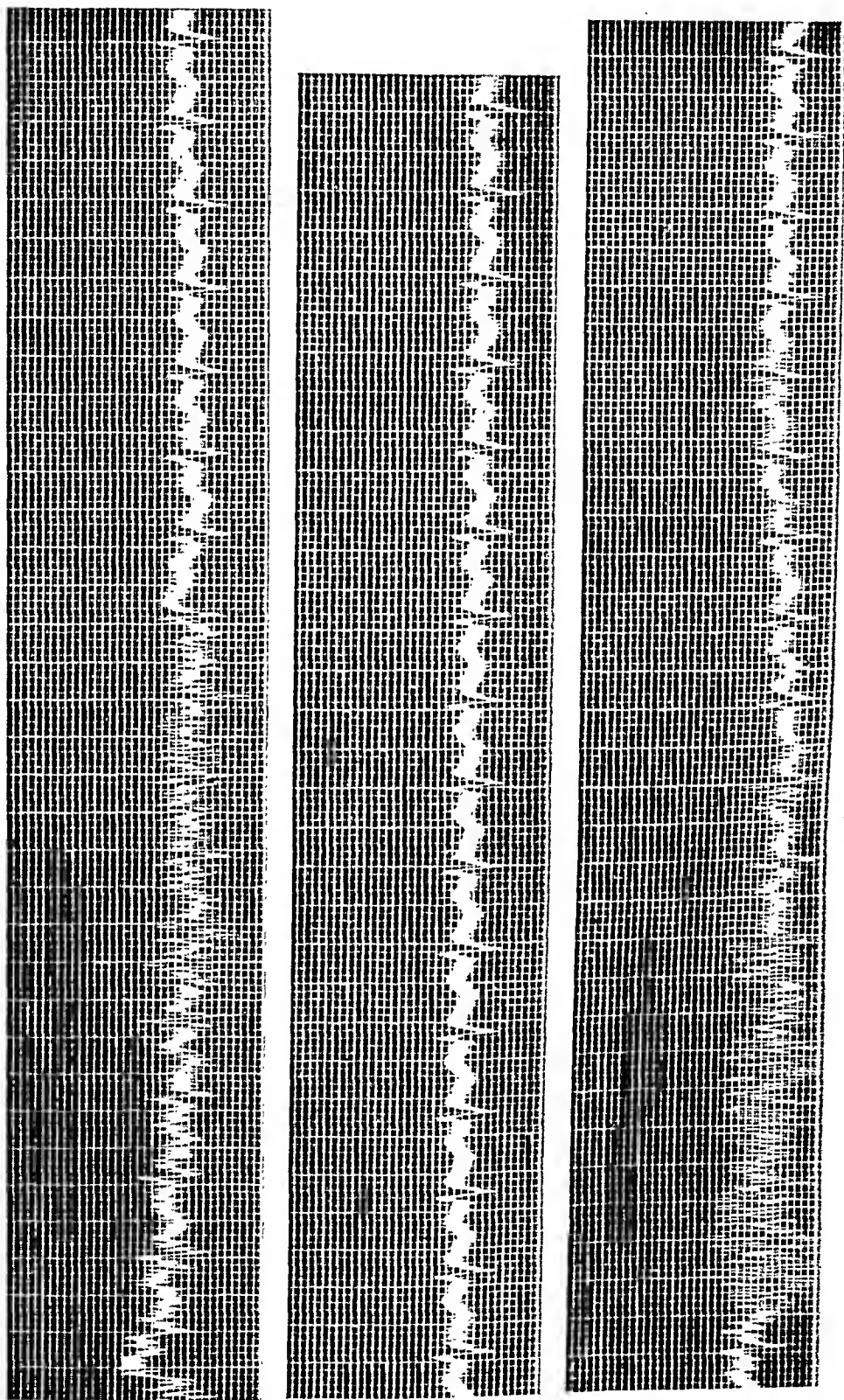


FIG. 2. (Continued.)

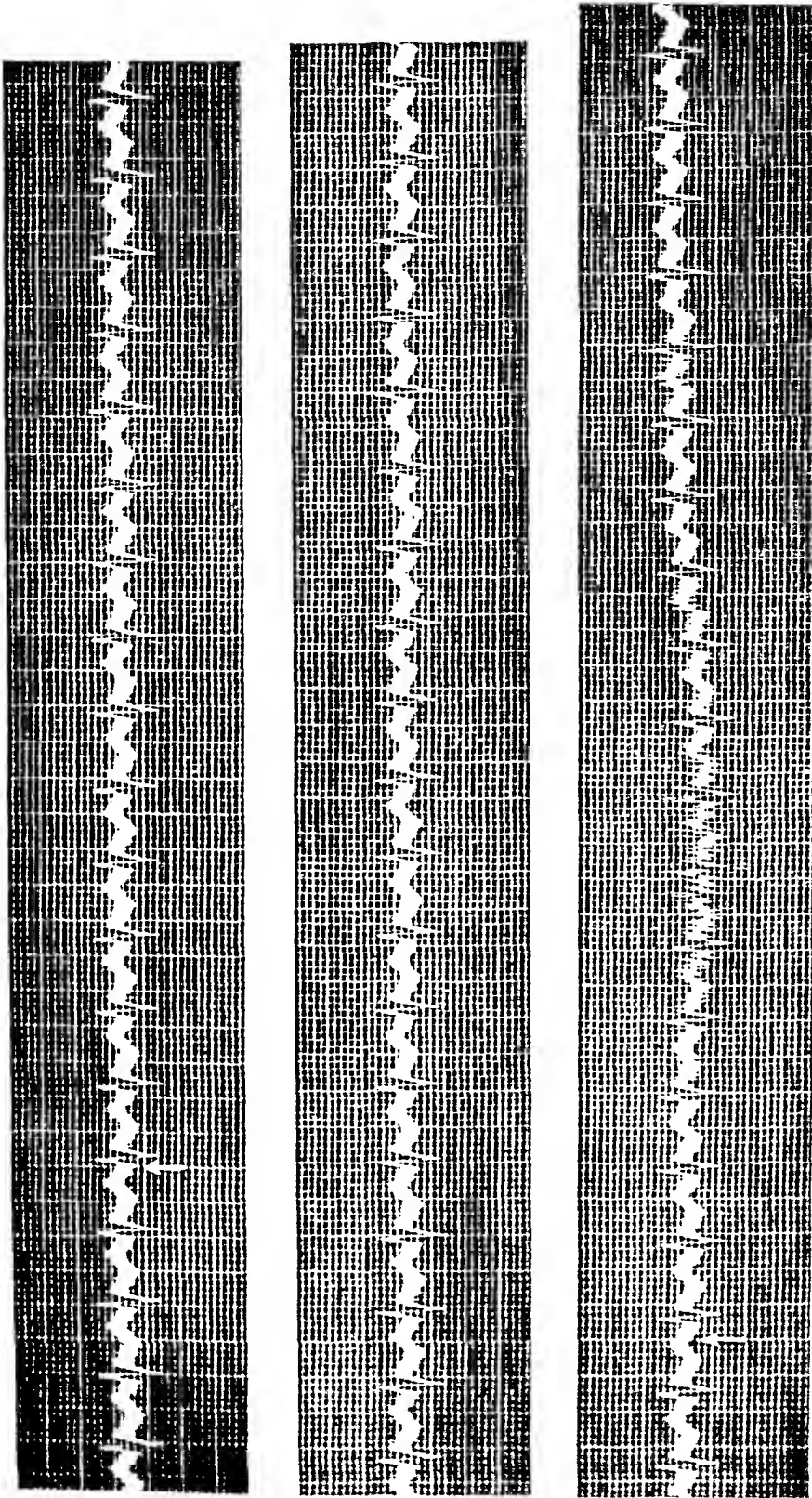


Fig. 3. Effect of compression of the left carotid sinus for 15 seconds after the patient was given  $\frac{1}{16}$  grain of atropine (Lead II). Arrows mark out time of compression (continuous record). Note convulsion following compression unassociated with any change in ventricular rate or other evidence of circulatory disturbance.



FIG. 4. Slowing of the ventricular rate following the compression of both eyeballs for five seconds (Lead II).  
Arrow represents when compression was stopped.

Compression of the right carotid sinus for one second caused, after a lag of two or three beats, a complete asystole lasting 2.4 seconds (figure 1). The onset of the asystole was abrupt, and the block was immediately complete. The offset, however, was gradual and extended over 4.6 seconds, during which time three ventricular systoles occurred, with a progressively improving A-V conduction. There was no change in the flutter rate during the entire period of observation. On recovery from the effects of the carotid sinus pressure, the ventricle resumed the pre-compression rate of 150. The same abrupt and rapid onset of asystole of the ventricles and the relatively gradual offset occurred with either gradual or abrupt compression of the right carotid sinus. Three-second compression gave rise to periods of asystole and relatively slow beating about twice as long as those obtained with one-second compression. Compression of the left carotid sinus gave results identical with those following compression of the right, except that the periods of asystole and slow beating were about one second shorter. In every case, on application of pressure the patient felt faint and lost consciousness almost simultaneously with the onset of asystole; this unconsciousness lasted during the absolute asystole, and disappeared during the period of slow beating. In the supine position, there was no well-defined pallor or flushing such as was noticed when the patient was erect.

Simultaneous compression of both sinuses in the supine position for three seconds gave results similar to those observed after compression of the right sinus alone in the erect position. Convulsions began after seven seconds of asystole, and these were identical with those previously described (figure 2, second, third and fourth strips). However, about 10 seconds after the end of the convulsion, when the pulse had returned to its pre-compression rate of 150, the patient had another convulsion less extensive and shorter than the first, but otherwise very similar in external appearance (figure 2, sixth strip). No blood pressure readings were made during these convulsions.

The patient was given atropine, gr.  $\frac{1}{16}$  hypodermically—a dose certain to abolish the vagus effects. There was no change in the auricular or ventricular rate after the patient was atropinized. Half an hour after the atropine was given each carotid sinus, and then both together, were compressed for three then five seconds, with no effect on the auricular or ventricular rates, no unconsciousness or sense of faintness. However, when either carotid sinus was compressed for 15 seconds, the patient had a small and short, but quite typical convulsion, during which time he again felt as though he were fainting (figure 3, third strip). This occurred without change in the pulse; no blood pressure readings were obtained. He could not be prevailed upon to sit up and permit us to repeat this procedure.

In short, it appears that in this patient the abolition of the ability of carotid sinus stimulation to cause asystole of the heart did not entirely abolish its ability to cause convulsions. This, and the fact that after bilateral sinus compression there occurred a convulsion without coincident asystole (figure 2, sixth strip), suggest that the mechanism causing convulsions and that causing cardiac asystole are not identical.

The use of atropine in doses adequate to abolish any cholinergic stimulation following carotid sinus compression<sup>1,2</sup> served several purposes. It demonstrated that the asystole of the heart was due to an action of the vagus on the A-V conduction system. In addition, it showed that the flutter was probably

not a transient one due to tonic carotid sinus activity; carotid sinus pressure may give rise to transient runs of auricular flutter.<sup>3</sup> The use of atropine also indicated that the convulsions were not entirely related to the asystole, but could occur without it, either, as thought by some, as a result of reflex constriction of the cephalic vessels<sup>4, 5, 6, 7</sup> or of some other obscure neurogenic process. A vasomotor dilatation with drop in blood pressure and resultant cerebral anemia was not absolutely ruled out, but the absence of any change in the pulse makes this unlikely. Finally, the use of a large dose of atropine showed that this drug itself is probably not sufficient to bring about 1 to 1 conduction in auricular flutter, although it may increase the ventricular rate when the conduction ratio is low<sup>8</sup> just as it prevents the lower conduction ratios during carotid sinus stimulation.

The effect of carotid sinus pressure on the heart with fluttering auricles is not uniform. The slowing of the ventricular rate is not a constant occurrence even in cases where the heart can be slowed by ocular pressure.<sup>9, 10</sup> This failure to elicit slowing may be due to an inability to locate the carotid sinus, whose position in the neck is not constant.<sup>11</sup> It is generally agreed that carotid sinus stimulation slows the ventricular rate in auricular flutter by increasing the A-V conduction time up to complete block.<sup>9</sup>

There is somewhat more variation of opinion concerning the effect of vagus stimulation on the fluttering auricles. Clinically, most observers using ocular or carotid sinus pressure report that there is no vagus effect on the auricles in auricular flutter.<sup>10, 12, 13, 14, 15</sup> Others, however, using similar methods, as well as direct stimulation of the vagus nerve in the dog, have reported either an increase in the flutter rate<sup>16, 17</sup> or a change in the configuration of the auricular waves.<sup>18</sup> In the case here presented, where an extremely active and sensitive carotid sinus mechanism was present, we felt that any vagus effect on the auricles, if it existed, would be exaggerated. However, no change was observed either on the rate of the auricular flutter or on the configuration of its waves.

It is interesting to note in this case the almost equal effectiveness of the two carotid sinuses in producing A-V block, and their equal ineffectiveness on the auricles. It is probable that the auricular flutter and hyperactive carotid sinus are coincidental. It is true that in persons with generalized arteriosclerosis and coronary sclerosis the carotid sinus reflex tends to be more active than in other age groups,<sup>19</sup> and that this is the group in which one frequently sees auricular flutter, often with no other evidence of heart disease.<sup>20</sup>

The oculo-cardiac reflex was less effective in our case than the carotid sinus reflex; nor did it appear to be enhanced by the presence of a hyperactive carotid sinus reflex (figure 4). There was definite evidence that the activity of the carotid sinus of our patient was abnormal. In the first place, very brief sinus compression quickly led to asystole of considerable duration, as well as to convulsions. Second, the sequence of events in this case was very similar to that following carotid sinus pressure in patients having known hyperactive carotid sinuses and sinus rhythm.<sup>21, 22</sup> While it is possible that the earlier fainting spells before the last admission represent an auricular flutter with periods of 1 to 1 conduction,<sup>23</sup> or paroxysms of auricular flutter, this is unlikely in view of the mechanism found during the patient's last hospital stay.

## SUMMARY

We have presented a patient with a hyperactive carotid sinus and auricular flutter. We have been able to show that the flutter was not due to a tonic activity of the vagus, and that even in the presence of a hyperactive carotid sinus mechanism vagus stimulation does not affect auricles which are fluttering. Finally, in this case we were able to demonstrate that the patient's convulsions, which appeared when either carotid sinus was stimulated, were not entirely due to the asystole which the stimulation brought about.

We are indebted to Dr. L. Block for permission to report this case, and to Dr. L. N. Katz for his suggestions in analyzing the mechanism and in preparing the report.

*Note:* While this paper was in press, the patient came in for fulguration of his bladder tumor; soon thereafter he developed frequent fainting spells and convulsions. Electrocardiograms revealed these to be due to paroxysmal ventricular flutter and fibrillation; one of these was irreversible and the patient died. No autopsy was obtained.

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## A CASE OF ACUTE IDIOPATHIC HEMATOPORPHYRIA WITH ACUTE ASCENDING PARALYSIS \*

By HAROLD W. PALMER, M.D., F.A.C.P., *Wichita, Kansas*

IN 1911, in his original monograph, Günther<sup>1</sup> described a rare constitutional disturbance which he called hematoporphyrinuria, the essential symptom of which was the finding of large quantities of hematoporphyrin in the urine. He later made the statement, confirmed by Hoppe-Seyler, that hematoporphyrin was not the pigment found in the urine in this disease, but that the pigments actually were coproporphyrin and uroporphyrin, related substances. However, through general acceptance by Garrod and others, the pigment is still referred to as hematoporphyrin and the disease state as hematoporphyrinuria. In 1925 Günther<sup>1</sup> attempted to classify the hematoporphyrinuria into three separate groups, namely, (1) congenital hematoporphyrinuria, (2) acute idiopathic hematoporphyrinuria, and (3) acute toxic hematoporphyrinuria. Of the first group, the congenital, he was able to collect 18 reported cases, to which Mason and Farnham,<sup>2</sup> reviewing the literature in 1931, were able to add six cases, bringing the total to 24. The characteristics of this group are that large quantities of hematoporphyrin are found in the urine often associated with other unidentified pigments together with a bullous eruption on the exposed surfaces of the skin following exposure to sunlight. These cases are found in children and young individuals and the condition may be present from birth. The disease is often familial and in recent reports, at least in isolated instances, seems to follow Mendelian lines.<sup>3</sup> The skin lesions may be quite deep seated with intensive scar formation and mutilation of parts affected. Often cases showing so-called pink teeth are noted, the teeth being stained brown or pink. Enlargement of the spleen is often an associated finding, as is also a moderately severe secondary anemia.

The second group defined by Günther<sup>1</sup> contains the acute idiopathic type of case. In this group he referred to 18 proved cases; but Mason, Courville and Ziskind,<sup>4</sup> reviewing the literature in 1933, were able to bring the total to 46 authenticated cases.

Of the third group, the acute toxic type, Mason, Courville and Ziskind<sup>4</sup> were able in 1933 to find 100 cases. Of these 86 had used sulphonal and 11 had used trional. Lead, veronal and other barbiturates have been reported as etiological

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From the departments of Medicine and Pathology, Wichita Hospital, Wichita, Kansas. I wish to express my gratitude to Dr. C. A. Hellwig, Chief of Pathological Service, St. Francis Hospital, Wichita, Kansas, for his very able assistance and advice in the study of the histopathology in this case.



agents. Clinically the two groups, the acute idiopathic and the acute toxic, are identical except that in the former the etiological agent is unknown whereas in the latter a history of the excessive use of sulphonal, trional or other barbiturate is found. Lead has also been reported as a toxic agent in this group.

Because acute idiopathic hematorporphyria is relatively a rare disease it was thought that a clinical case report with autopsy findings would be of interest. Mason, Courville and Ziskind<sup>4</sup> state that they found in 1933 that only 12 of the 46 reported clinical cases had come to autopsy.

#### CASE REPORT

Mrs. L. H., white female, aged 26, was admitted to the hospital June 28, 1938, with the history that about 10 days previously her acute illness had begun with pain in the back. The pain was described as severe, requiring morphine for relief. Shortly after this she complained of burning pain in the bottom of her feet, this

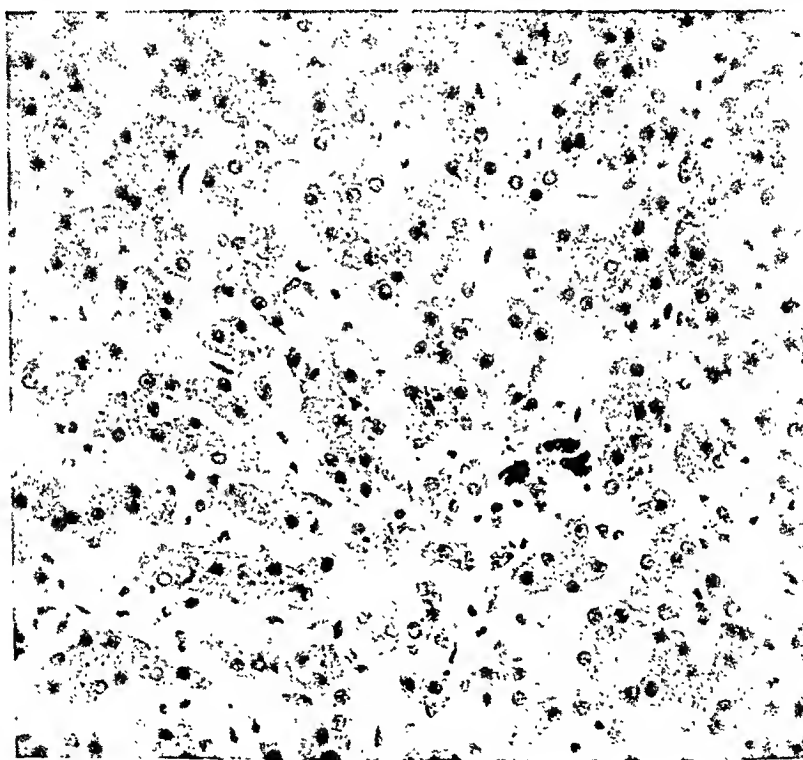


FIG. 1. Section of liver showing marked degenerative changes of the cords with stippling of the K pffer cells and larger amorphous pigment deposits. Hematoxylin and eosin stain. Magnification  $\times 280$ .

being followed by complete loss of use of the legs accompanied by intense pain in all the leg muscles. A few days later the paralysis had progressed to the arms, accompanied by intense pain in all the arm muscles. The generalized paralysis was accompanied by spasmodic twitching of all the involved skeletal muscles. There was no history of the use of sulfonal, veronal, trional or exposure to lead.

Her past history showed that she had always been nervous and underweight. At 16 years of age she had had an acute illness with abdominal pain and vomiting which was thought to have been a liver disturbance, but no jaundice was noted at



that time. The color of the urine at that time was not observed. At 20 years of age she had a Bell's palsy, the duration of which was about six weeks. At the age of 22 she had married and had had her first pregnancy which was uneventful. The hospital record shows the urine to have been normal in color at that time. During the course of her second pregnancy at 23 she frequently noted that the urine was dark brown in color. She had nausea and vomiting for the first three months of

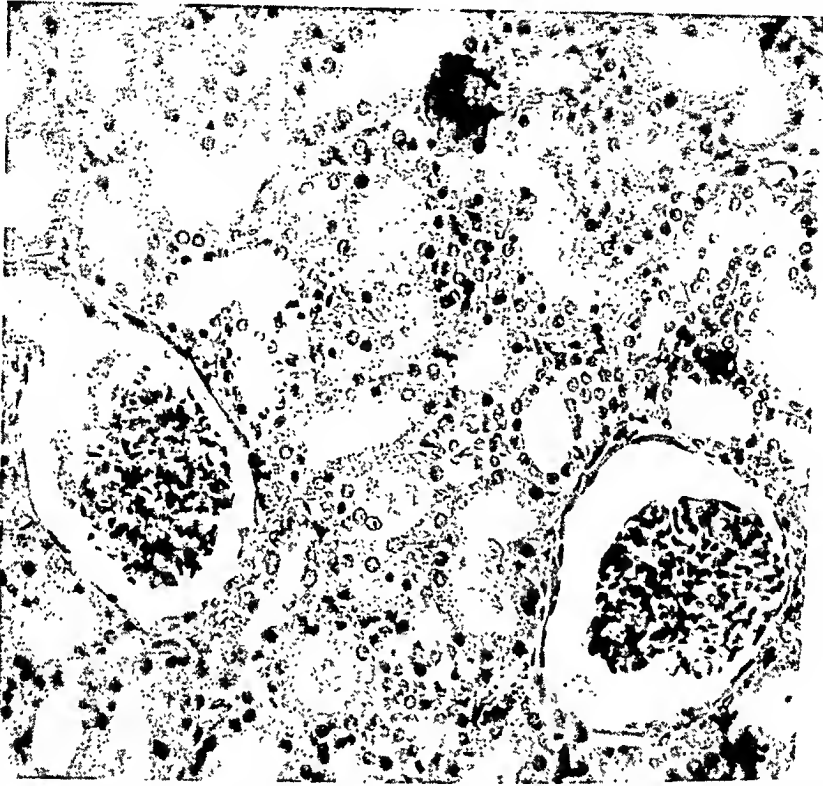


FIG. 2. Section of kidney showing marked degenerative changes in tubular epithelium and glomeruli with deposits of pigment in the epithelium of the tubules and in the glomeruli. Hematoxylin and eosin stain. Magnification  $\times 280$ .

this pregnancy but again delivered at term normally. The hospital record again shows the urine normal in color at the time of this delivery. About three months previous to the present admission she had had a miscarriage, when she was about three months' pregnant, from which she made an uneventful recovery without surgical interference.

On examination she was very thin, emaciated and dark skinned, weighing not more than 90 pounds. No jaundice was present. There was complete paralysis of all the muscles of the arms and legs with marked atrophy of all groups. A bilateral wrist and ankle drop was noted. There was marked tenderness to slight pressure over all the skeletal muscles, but cutaneous sensibility to pain, heat and cold stimulation was normal and she readily identified common objects placed between the fingertips. All deep tendon reflexes were absent except that of the right tendon Achilles which was present and active. The Babinski sign was negative on both sides. Respiration was deep and labored although no actual air hunger or cyanosis was apparent. Difficulty in swallowing was noted even with water, and choking resulted when liquid was taken rapidly. Articulation was difficult and the speech might be described as being explosive in character.

Examination of the external ocular muscles was negative, but there was a slight ptosis of the left upper lid. The pupils were large but reacted to light and accommodation. The eye grounds were normal. The tongue protruded in the midline with slight tremor. The ribs were plainly visible through the chest wall because of the lack of subcutaneous fat. The heart and lungs were entirely normal. The pulse was constantly rapid with an average rate of about 120 per minute. The blood

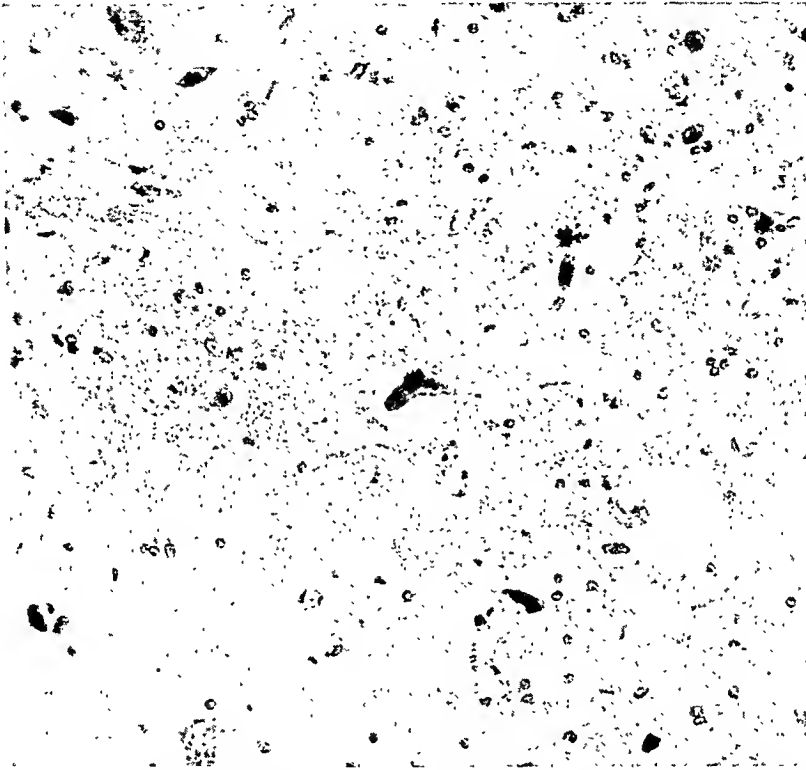


FIG. 3. Section through anterior horn of the spinal cord showing marked pyknosis of the anterior horn cells with diffuse deposits of pigment. Hematoxylin and eosin stain. Magnification  $\times 280$ .

pressure was 106 systolic and 70 diastolic. The abdomen was sunken, and the iliac crests prominent. The spleen and liver were not palpable and no masses were felt. Examination and inspection of the vagina, cervix and pelvic contents was negative.

*Laboratory Examination:* The red blood cell count was 3,960,000 and hemoglobin 80 per cent (Newcomer). The white blood cell count was 9,500 and the differential showed 63 per cent polymorphonuclear cells, 15 per cent band forms, 15 per cent lymphocytes, 5 per cent metamyelocytes, 1 per cent basophiles, 1 per cent eosinophiles. The color of the urine varied from a reddish brown to brownish black. The specific gravity ran from 1.013 to 1.022. All examinations for albumin, sugar, bile, acetone and diacetic acid were negative. Urobilin was found in large quantities. The spectroscopic examination by Garrod's method showed the characteristic absorption bands for hematoporphyrin on two different occasions. Examinations for blood, blood pigment and iron were negative. The spinal fluid pressure was low, the fluid was clear and contained no cells and no globulin. The Lange test was negative. The fragility test on the red cells was normal, showing beginning hemolysis at 0.42 per cent NaCl concentration. The blood serologic and chemical tests were as follows:

Wassermann on both blood and spinal fluid was negative.

Blood sugar: 129 mg. per 100 c.c. of blood.

Blood calcium: 11 mg. per 100 c.c. of blood.

Blood cholesterol: 144 mg. per 100 c.c. of blood.

Blood urea: 72 mg. per 100 c.c. of blood.

Blood creatinine: 1.3 mg. per 100 c.c. of blood.

No basophilic stippling (lead) was noted and no arsenic could be demonstrated in the urine.

**Course:** The temperature at no time was over 99.2° F. and for the most part was below 98.6° F. The pulse remained rapid, ranging from 110 to 130 per minute. Breathing gradually became less labored and on discharge from the hospital August 5, 1938, 38 days after admission, swallowing of liquids and soft foods was normal. Constipation was a prominent symptom and only on one or two occasions was lack of sphincter control for urine and feces recorded. At the time of discharge from the hospital the peripheral sensory examination was still normal. Some improvement in the motor paralysis was noted but the degree of recovery was not marked. Mentality was clear until a few hours before death and at no time during the course of the disease were hallucinations or delusions noted. Pigmentation of the skin, especially over the hands, was quite marked for a period of two weeks previous to death. She died at her home on August 22, 1938, about two months after the onset of her acute illness.

**Therapy:** Morphine was used for the relief of pain, salicylates proving of no value. During the stage of partial bulbar paralysis nutrient proctoclysis was resorted to. Vitamin B concentrate was administered with the hope that it would have a beneficial effect on the neurological lesions. No calcium was given in this case, although beneficial results have been reported from its use intravenously.<sup>3</sup>

**Autopsy:** The autopsy was performed about six hours after death. The body was that of a very emaciated young white female. The skin was almost bronze in color, the pigmentation being most marked on the hands. Numerous small cutaneous blebs were noted over the abdomen. There was no evidence of jaundice present. The pericardium contained about 50 c.c. of thin clear yellow fluid, and the surface of the heart was smooth. There was no hypertrophy of this organ and the valves were all normal. The lungs contained air except in the dependent portions where some bloody fluid was present. There were no pleural adhesions and no areas of gross consolidation were noted. The liver was slightly enlarged and had a deep reddish brown color. The surface was smooth and the cut section showed the same deep pigmentation as the surface. The gall-bladder contained one small soft cholesterol stone. The pancreas showed no abnormalities. The spleen was about twice average size and the cut surface was deep red in color. The pulp scraped easily. The bladder was opened and contained about 50 c.c. of a dark red urine. The wall of the bladder was slightly thickened. There were no gross abnormalities in any of the pelvic organs. The gastrointestinal tract was negative except for a large fecal mass in the rectum. The kidneys were normal in size and consistency but also showed the reddish brown color both on the surface and on cut section. The adrenals showed no unusual changes. On exposure of the brain, the meninges and convolutions showed no gross pathological alteration. The ventricles were not dilated. Blocks were taken from the internal nuclei on either side and in the region of the third ventricle. Also blocks were taken from the pons, cerebellum and various portions of the brain stem. The spinal cord was exposed and blocks were taken at frequent intervals along its entire length. Blocks were taken from the left popliteal nerve and from the left brachial plexus.

**Histopathology:** Heart: All sections showed poor staining of the cross striations of the fibers. In some areas interstitial round cell infiltration was noted while in

others hemorrhage was present in the interstitial spaces. Fatty degeneration of the muscle fibers was quite evident in some of the sections.

Liver: A high degree of diffuse cloudy swelling was present going on to almost complete atrophy of the cords in some areas. The Küpffer cells showed extensive stippling with pigment which on differential staining with Prussian blue was found to be iron containing. Larger amorphous masses of iron free pigment as differ-

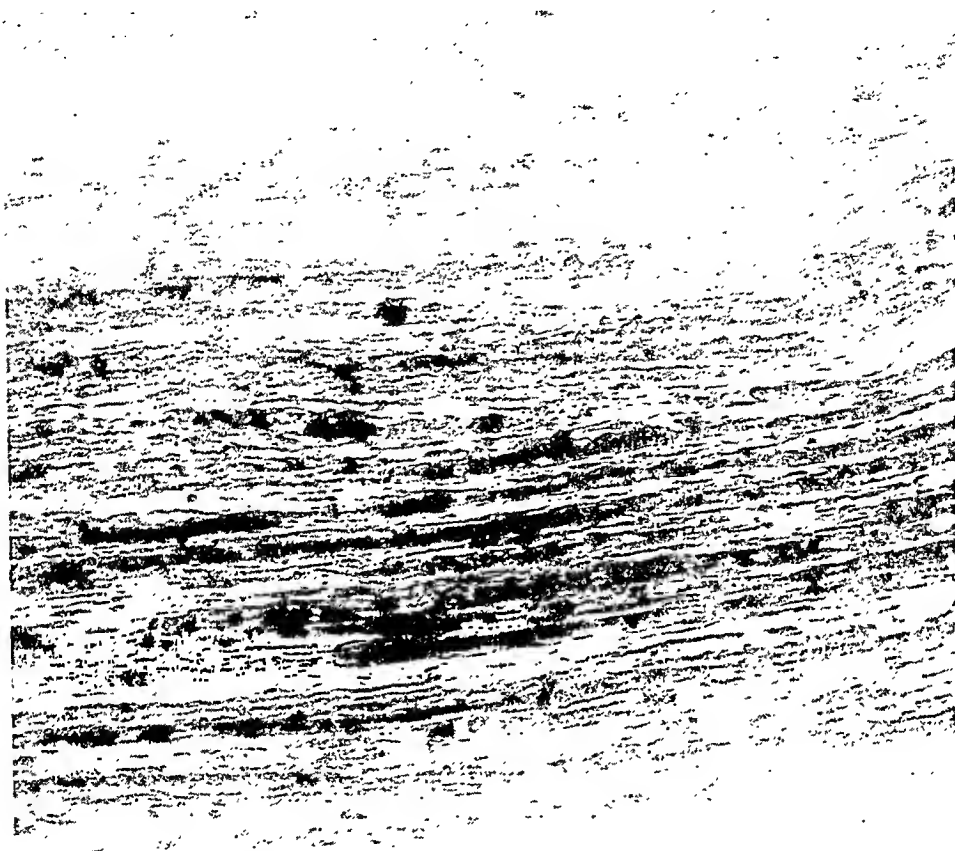


FIG. 4. Longitudinal section popliteal nerve showing moth-eaten appearance of myelin sheaths. Speilmeyer stain. Magnification  $\times 280$ .

entiated by Prussian blue staining were also found in the Küpffer cells in all the sections. There was a perivascular round cell infiltration noted in some areas and in others groups of round cells were seen in the interstitial tissue.

Spleen: Large amorphous masses of pigment were scattered throughout all the sections. The malpighian corpuscles were small and widely separated, and the reticulum cells were few in number.

Pancreas: No pathological alteration was noted in any of the sections except that the islands of Langerhans were relatively few in number.

Kidneys: Both organs showed the same pathological alterations. There was a marked diffuse cloudy swelling of the epithelium of the tubules which in some areas was so marked as to be classified as complete atrophy. The glomeruli showed the same degenerative changes but to a far lesser extent. Amorphous masses of pigment were noted in the cytoplasm of the epithelial cells of the tubules and to a lesser extent in the glomeruli. Differential staining with Prussian blue showed this pigment to be almost entirely non-iron containing.

Lungs: Sections of the lungs showed no pathological alterations.

Central nervous system and peripheral nerves: The essential pathological alterations in the central nervous system were cytological. The cortical cells show marked pyknosis and in some areas vacuolization of the nuclei. Many showed no chromatin



FIG. 5. Longitudinal section popliteal nerve showing round cell infiltration. Hematoxylin and eosin stain. Magnification  $\times 280$ .

material and no nucleolus. Masses of amorphous pigment were noted in all sections, which by differential staining were shown to be iron and iron free pigment about equally divided. The motor cells of the anterior horns of the spinal cord and, to some extent, those of the posterior horns at all levels showed marked pyknosis and shrinking. Pigment was also found in all the sections of the cord examined, there being both iron and iron free pigment present. The Purkinje cells of the cerebellum showed definite signs of degeneration in that tigroid bodies were unstained or absent and many cells showed no staining of the nucleolus. The sections of the peripheral nerves showed in some areas marked degeneration of the myelin sheaths and in others extensive round cell infiltration. A few scattered phagocytic cells were noted which contained brown pigment.

## CLINICAL DISCUSSION

The onset in the acute cases, according to Mason,<sup>5</sup> is usually manifest by severe cramp-like pain in the abdomen, usually between the umbilicus and the pubis and occasionally radiating to the flanks, thighs or even to the chest. Usually there is a history of nervousness, easy fatigability, sleeplessness and vague abdominal pain preceding the initial attack by a few weeks or even a month. With the onset of abdominal pain, nausea and vomiting appear and constipation is the rule rather than the exception. Slight fever and moderate leukocytosis may be present. The abdomen is usually soft, but slightly tender to palpation. Roentgen-rays of the gastrointestinal tract show a dilated ileum, duodenum or a dilatation of some portion of the large bowel. With the advent of the acute attack the urine can be shown to contain urobilin, porphyrin and other pigments. The urine is a dark brown or burgundy wine color, giving a negative test for iron, and no erythrocytes are found in the sediment. Characteristic absorption bands for hematoporphyrin after the method of Garrod are found by spectroscopic examination. In the acute attacks ending fatally the nervous system shows definite involvement, with convulsions, states of delirium, and weakness of the extremities ending in an acute ascending paralysis with bulbar palsy and asphyxia. The disease occurs most commonly in the third and fourth decades although no age is exempt. The incidence is higher in women than in men, the ratio being about four to one. The prognosis in acute idiopathic hematoporphyria is extremely grave, 50 per cent dying with the first acute attack. In cases with involvement of the central nervous system the mortality is even higher.

In this case it is interesting to note that at no time during the acute illness was abdominal pain complained of nor was there abdominal distention or vomiting. Also death was not due to bulbar paralysis but undoubtedly resulted from toxemia, although bulbar symptoms were present for a time. The clinical picture of ascending paralysis here corresponds quite well with the toxic type of Landry's paralysis described by Drake<sup>6</sup> and others.

## PATHOLOGICAL DISCUSSION

The pathological findings in this case agree quite well with the findings of Mason, Courville and Ziskind<sup>4</sup> on their two autopsied cases except that they do not report enlargement of the spleen. The degenerative changes in the motor cells of the brain and spinal cord in this case would seem to be more advanced than their findings. The degenerative changes in the liver and kidneys would also seem to be more severe in this case. These differences might be explained by the fact that this patient lived about two months after the onset of the acute attack, whereas the duration of life in their cases from the advent of the acute attack was about one month. The degenerative changes in the Purkinje cells of the cerebellum and the changes in the myelin sheaths of the peripheral nerves with areas of round cell infiltration in the peripheral nerves are an almost exact counterpart of their findings.

## PATHOGENESIS

The pathogenesis of acute idiopathic hematoporphyria is not well understood. Günther<sup>1</sup> contends that the condition is an inborn error of pigment metabolism whereby the normal synthesis of hemoglobin is interfered with, accompanied by

excretion of porphyrin in the urine. It is thought that the acute condition is a result of an endogenous or exogenous intoxication accompanied in all probability by a peculiar susceptibility to the disease.

### SUMMARY

A case of acute idiopathic hematoporphyria with symptoms of an acute ascending paralysis is presented with autopsy findings. Clinically the case presents neurological findings similar to the toxic type of Landry's paralysis. Death in this case was believed due to toxemia and not to bulbar paralysis and asphyxia which is the usual mode of termination in cases with extensive central nervous system involvement. The paralytic symptoms are accounted for by degenerative lesions of the anterior horn cells of the spinal cord and changes in the peripheral nerves.

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## EDITORIAL

### *CERTAIN PROBLEMS CONNECTED WITH VOLUNTARY DISPENSARIES*

Voluntary dispensaries have greatly increased in size and complexity in our larger cities in the last decade and constitute a very important factor in the medical care of urban communities. In spite of this fact, dispensaries have not received their proportionate share of attention from those interested in broad programs for public health. Yet all physicians and welfare workers realize that the unusual load placed upon dispensaries during recent years has rendered it urgent to find some solution for a number of old and fundamental problems connected with these institutions.

A first problem arises from the tendency of the dispensary to assume the rôle of family physician for its clients, when in fact its organization, and its relation to the other factors in medical care, i.e., home care and hospital care, are not adapted for this purpose. There is usually an attempt on the part of dispensaries to arrange matters so that the same physician will see the patient throughout one series of admissions, but even this is difficult to arrange and often proves impossible. Repeated readmissions of the patient over a period of years for varied conditions in different clinics usually mean that the patient's case is handled from many angles by many physicians in succession or even simultaneously. Too often such medical efforts lack coördination.

Very few dispensaries, indeed a negligible percentage, are linked with any system of home medical care. This is a very distinct handicap in that the dispensary physician has no chance to observe his patient's illness in the home. The crux of a diagnostic problem may, for example, be the nature of some nocturnal attack. The dispensary physician will never observe it because home care is not his province. Moreover, the dispensary physician will not meet the family of the patient, nor estimate the influence of his home environment on his illness.

Most dispensaries are linked with a hospital, but this association is usually more physical, administrative, and economic in nature than medical. With many notable exceptions, it is true that a wide gap usually exists between the dispensary staff and the house staff. Rarely has the dispensary staff much voice in the decisions made by the house staff concerning the former dispensary patient. There are too many patients and too little time in most institutions for such conferences. Frequently, moreover, the dispensary patient can not find a bed in the hospital linked with his dispensary and so is lost to view in another hospital.

The indigent patient frequently, therefore, receives such home care as he gets through the generosity of the practitioner in his neighborhood; goes to the dispensary as an ambulant case and there comes under various dispensary



physicians, and when he needs hospitalization is admitted to a hospital ward where still another group of physicians takes charge of his case. When he is discharged he may again apply for help to the local practitioner. It is obvious that the patient has received medical care in this circuit but it is also plain that he must often feel the need of a medical advisor who knows his whole medical history as well as his home environment. The lack of this steadying influence is one cause for the failure of the average dispensary and hospital system of medical care to deal successfully with the psychoneurotic patient. Even in the simpler problems of organic disease the present system is often a wasteful, repetitious and inefficient one.

Patients are at times admitted to the hospital who could be cared for in the home at much less expense if adequate home care were available; and often too, patients after discharge from the hospital may lose much of the value of their stay or at least have a greatly retarded convalescence for lack of any follow-up treatment.

A multiplicity of physicians and of examinations is often necessary for the adequate diagnosis of obscure disease but a single medical director is an essential factor in efficient treatment of illness.

It is widely acknowledged that better integration of these three phases of medical care is desirable. Partial solutions of many sorts have been evolved such as the unit system of records which keeps the patient's dispensary and hospital record together in one folder; the interchange of ward and dispensary attending physicians, dispensary work by interns and residents, and joint conferences of the two staffs. The medical social service worker evolved as an attempt to improve the physician's knowledge of the patient's home environment and to ensure more adequate carrying out of the instructions given as to treatment.

There remains, however, a fundamental inefficiency in the splitting up of responsibility for the patient's welfare entailed by the present relative isolation of dispensary medical care from home medical care and hospital medical care. In Boston, Buffalo, Minneapolis, and perhaps elsewhere integrated systems combining home, dispensary, and hospital care are in operation. They are deserving of careful study by other cities.

Another major problem involving dispensaries is their economic status. The budget of the average dispensary is made up roughly of the usual items for maintenance of the building and equipment, the cost of medical supplies, the salaries of non-professional personnel and a limited number of professional salaries. The bulk of the medical work, often all of it, is done without compensation by voluntary physicians. In addition there are often volunteer aides to the nursing and social service departments.

When voluntary dispensaries were smaller the voluntary hospital usually provided all the funds needed by the dispensary from its general income or from special gifts for this purpose. As the voluntary dispensaries grew in size the hospitals sought special appropriation for the free care given to patients in these units. But with considerable unanimity City and County

governments have failed to provide such support. In some cities Community Chests have given special support to dispensaries, but this is exceptional. In general, however, the support is derived about as follows: A small fee is charged all patients for admission and a further charge is made for medicines, roentgen-rays, etc. The fee is less than the usual charges for medical attention, special examinations, drugs, etc. and patients unable to pay are not turned away. In the Hospital Survey for New York the figure given for the average patient's fee in New York dispensaries is "about fifty cents" and it is estimated that this represents "about half of the cost to the institution of the service rendered, without including any item of expense for physicians' services." The deficit is paid by the hospital from its general funds.

There are at least two serious defects to this system. Partly because of the inclusion of part-pay patients as admissible clients the number applying for dispensary treatment has greatly increased. As a result the quality of the work tends to decrease. To avoid this danger the dispensary is driven to the appointment system, in other words, the dispensary turns some away.

The capacity of the dispensary to look after indigents is lessened since to survive financially a certain number of appointments must be given to part-pay patients. Moreover, such a system of admitting part-pay patients raises the problem of competition with the outside practitioner. Finally it demands of the voluntary dispensary physician not only that he shall care for the indigent without charge, but that he shall assist the hospital, by his professional work with part-pay patients, to earn money to support the dispensary in which he treats these indigents.

There is another aspect to the economic support of voluntary dispensaries which is equally unsatisfactory. The money received from patients is usually less than a half of the total money cost of the dispensary to the parent hospital. The rest must be found as a rule from general hospital receipts, just as the usual deficit on free ward cases must be found from these same receipts. Except in the cases of heavily endowed hospitals this means that the hospital must make sufficient profit on its private and semi-private accommodations to finance the deficit on the ward cases and on the dispensary. Part of the high cost of medical care in catastrophic illness, for people of moderate means, of which so much has been said, is due to the fact that such patients in many instances during their hospital stay pay not only for themselves but towards the cost of the wards and dispensaries. Medical care for the indigent is financed in part by what amounts to a special tax laid upon those already burdened with their own illness and its economic consequences.

A third problem arises which is connected with the teaching function of the dispensary. The clinical training of undergraduate students in the various clinics of medical school dispensaries is a well established function of these institutions. The training of the dispensary staff physician is often provided for in the best organized clinics. In smaller dispensaries, however, the Chief of Clinic, confronted with a scarcity of assistants and a large num-

ber of patients, is often forced to give all his available time to the examination of patients and has none left to devote to teaching of his assistants. Assistant physicians tend to drop out of clinics in which they do not get the educational benefit of consultation and conference on the problems presented by their patients. It is difficult to find in any city sufficient skilled clinicians with administrative and teaching ability to fill the positions as Chief of Clinic in the numerous clinics of each of the various dispensaries. This difficulty is not lessened by the disheartening lack of adequate facilities for the best work which prevails in a large number of impoverished dispensaries, nor by the fact that the position of Chief of Clinic in a dispensary rarely carries any salary. The potential rôle of the dispensary as a center of continuous postgraduate instruction is at present far from fully realized.

It seems evident that the dispensary, originally an emergency type of institution for palliative medicinal treatment of the sick poor, has vastly increased its clientele and the scope of its medical work, but that (1) the rôle that it should play in a system of medical care needs careful reconsideration; (2) its present inequitable system of financing should be abolished; and (3) its development as a postgraduate school for the practitioner should be planned and fostered.

M. C. P.

## REVIEWS

*Roentgen Technique.* By CLYDE McNEILL, M.D. 315 pages; 14.5 × 23.5 cm. Charles C. Thomas, Springfield, Illinois. 1939. Price, \$5.00.

The positioning of a patient for a roentgen examination which most clearly demonstrates abnormalities, is an art developed by careful and patient effort, combined with a thorough knowledge of roentgen anatomy and pathology. The close supervision of roentgen technic by the roentgenologist makes for thorough diagnostic roentgenology which eliminates, to a high degree, the chance of error due primarily to faulty technic. The author is primarily concerned in this book with the positioning of the patient, but suggests other factors in the production of good diagnostic films. As far as possible such factors of technic as voltage, milliamperage, and exposure time are not discussed. These latter mentioned factors can be wisely disregarded in such a volume since they are constantly changing with the advent of new apparatus, and since they must be adjusted to the capacity of any given apparatus.

The author has arranged the material in a very concise and unique fashion. Generally speaking, there is a photograph of the patient positioned for the roentgen examination of a part in the upper half of the left hand page. Below this, is placed a neatly labelled drawing of the roentgenogram obtained. On the opposite page a list of some of the technical factors is presented followed by a detailed description of the position of the patient and the course of the central ray. With this description there is also a short discussion of the values and limitations of the particular position and in some instances, a list of references is furnished for those who wish to investigate further.

The book is quite complete, including such procedures as the visualization of the heart and great vessels by diodrast, cephalopelvimetry, lipiodol studies of the spine, and tonography.

The photographs and drawings are numerous and well reproduced. The paper and printing are excellent.

Dr. McNeill's work will be an asset to the library of anyone doing diagnostic roentgenology, and it is highly recommended for study, and as a reference.

W. L. K.

*The Neurogenic Bladder.* By FREDERICK C. McCLELLAN, M.S., M.D. xvi plus 206 pages; 15 × 24 cm. Charles C. Thomas, Springfield, Illinois, and Baltimore, Maryland. 1939. Price, \$4.00.

In recent years there has been such widespread interest in the physiology of the bladder that a monograph of this type is of particular value at this time. Anyone who has the time to search the English and American literature will, of course, find all that the book contains, but the author has presented a readable and practical summary of this extensive research.

In the early chapters the author discusses the anatomy and neurophysiology of the bladder. The spinal cord pathways are discussed, and he gives a very useful classification of the neurogenic bladder. The technic of cystometric study is clearly covered, together with a description of the various types of cystometers now in use. The concluding chapters deal with the treatment of the neurogenic bladder, and there is a very useful summary.

Five hundred cystometric studies were done by the author, and he has analyzed approximately 200 neurogenic bladders. The appendix includes a synopsis of 100 of these cases, and there are 49 graphs illustrating various types of bladder dysfunction. The bibliography consists of 118 well chosen titles. The book is to be highly recommended.

J. G. A., JR.

*Medical Microbiology.* By KENNETH L. BURDON, Ph.D., Assistant Professor of Immunology and Bacteriology, Louisiana State University, School of Medicine. 763 pages; 15 × 23 cm. The Macmillan Company, New York. 1939. Price, \$4.50.

This is an amplified edition of the author's "Textbook of Bacteriology." As is stated in the preface, it is the intention to reach fundamentals. For the pre-medical student it should be most valuable. To those who are studying nursing there is excellent material, but the book covers more of the intricacies of the subject than may be necessary in the short time allowed in their curricula. Its arrangement is unique and is most commendable, since the region of the body affected by the various micro-organisms is emphasized. This is a marked improvement although it may seem arbitrary in certain cases. The usual textbook style is avoided. From many stand-points this book can be highly recommended.

J. G. McA.

*Trauma and Internal Disease.* By FRANK W. SPICER, A.B., M.D., F.A.C.P. 593 pages; 16 × 23 cm. J. B. Lippincott Co., Philadelphia. 1939. Price, \$7.00.

This book collates and presents a new etiologic factor in internal medicine. As is necessary in such a pioneering work it brings together material from divergent sources. Many quotations and most examples have a legal tang. The quality gradient from example to example, and authority to authority is at times precipitous. The sections are compactly organized, with outlines and summaries for each chapter. To individuals engaged in medico-legal work this compilation will be of real help. The references are plentiful. To internists interested in acquiring a different perspective on their specialty it can be recommended.

C. A.

*A Text Book of Bacteriology: The Application of Bacteriology and Immunology to the Etiology, Diagnosis, Specific Therapy and the Prevention of Infectious Diseases for Students and Practitioners of Medicine and Public Health.* By HANS ZINSSER, M.D., Consulting Bacteriologist to the Peter Brigham Hospital and the Children's Hospital, Boston, and STANHOPE BAYNE-JONES, Professor of Bacteriology and Dean, Yale University Medical School, Master of Trumbull College, Yale University, New Haven, Conn. 990 pages; 17 × 25 cm. D. Appleton-Century Company, New York. 1939. Price, \$8.00.

The eighth edition of this standard text bears definite marks of revision. Much of the older, out-of-date material has been omitted. A certain haziness in the phraseology here and there has been clarified. The authors have availed themselves of the opportunity to introduce much new material. Thus sulphanilamide and its action are discussed and the chapters on streptococci and the viruses, among others, show the handiwork of the reviser. The section on the protozoa has been omitted. The book will serve well its purpose as a text for students of medicine and public health.

F. W. H.

*Man Against Himself.* By KARL A. MENNINGER, M.D. 485 pages; 15 × 22 cm. Harcourt, Brace, and Company, New York. 1938. Price, \$3.75.

Dr. Menninger's psychoanalytic study of self-destructive tendencies in man is divided into six sections. Each chapter is summarized. Like everything that Dr. Menninger writes, it is clear, extremely easy reading, and designed both for physicians and for the intelligent laity. It is a book that we can well imagine many patients reading with profit.

The first part takes up destruction in general; the second, the attitude toward suicide and the motives behind it; the third, various forms of chronic suicide such as

neurotic invalidism, alcohol addiction, and various types of behavior which increasingly cut the individual off from his social group; the fourth, focal suicide, deals with self-mutilations, malingering, polysurgery, purposive accidents, and impotence and frigidity; part five is an extremely interesting discussion of chronic suicide, that is, the part that psychological factors play in the development and course of chronic disease; the sixth section deals with reconstruction, that is, therapeutic technics.

Dr. Menninger feels that all self-destructive attempts are motivated by a disturbance in the balance between primary constructive and destructive instincts, that is, between a life instinct and a death instinct. In all classes of acute, chronic, or sub-total suicide he finds in the individual a wish to kill or an aggressive component, a wish to be killed expressing a need for self-punishment, and a wish to die, all three colored by a distinct, ever-present erotic element.

Those persons who are opposed to psychoanalysis will find many statements to strengthen their opposition. There are many points in the theory which large numbers of people will find it impossible to accept since his evidence and, for that matter, the study itself, is purely a psychoanalytic one.

In various places in the book he takes up anthropological questions, giving taboos and customs of savage tribes in support of his arguments. This we find difficult to accept since after all savages are integrated with their own civilizations, whereas the distinguishing feature of the psychotic individual in any social group is his failure to integrate himself with that group. In dealing with "organic suicide," he summarizes by saying, "Some forms of organic disease represent structuralization of perverted functions forced upon these organs to solve unconscious conflicts, the nature of these conflicts being related to the opposition and interaction of aggressive, self-punitive, and erotic components of the self-destructive tendency. The hypothesis is that organic lesions, so frequently requiring as they do direct agents from the environment such as bacteria or trauma for their initiation, differ not only in this respect but also in certain psychological respects from so-called functional disorders, mainly in that the sacrifice demanded by the destructive tendencies is a greater one and that the conflict is more strongly and deeply repressed, i.e., less accessible to consciousness."

Of the several studies of suicide which have appeared recently we find in this more food for thought than in any of the others. It is well worth reading.

H. M. M.

## COLLEGE NEWS NOTES

In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1940-41, are herewith announced and published:

President-Elect ..... Roger I. Lee, Boston, Mass.  
First Vice President ..... Robert A. Cooke, New York City  
Second Vice President ..... James G. Carr, Chicago, Ill.  
Third Vice President ..... Henry M. Thomas, Jr., Baltimore, Md.

The election of nominees shall be by the members of the College at its Annual Business Meeting, Cleveland, Ohio, April 4, 1940. These nominations do not preclude nominations made from the floor at the Annual Meeting itself. Nominations for members of the Board of Regents and members of the Board of Governors will be presented at the Annual Business Meeting.

Respectfully submitted,  
CHARLES E. WATTS, Seattle, Wash.,  
JAMES J. WARING, Denver, Colo.,  
CLARENCE L. ANDREWS, Atlantic City, N. J.,  
WILLIAM J. KERR, San Francisco, Calif.,  
SYDNEY R. MILLER, *Chairman*, Baltimore, Md.,  
*Committee on Nominations*

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### NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership and their Initiation Fees and Life Membership payments have been added to the permanent Endowment Fund of the College:

Dr. Anthony Bassler, New York, N. Y.  
Dr. Samuel A. Brown, New York, N. Y.  
Dr. George B. Crow, Burlington, Iowa  
Dr. Horace K. Richardson, Stockbridge, Mass.  
Lt. Comdr. Thomas F. Duhigg, (MC), U. S. Navy  
Dr. William S. Kerlin, Shreveport, La.  
Dr. Charles T. Way, Cleveland, Ohio

The Life Membership plan of the College, whereby members may underwrite their future dues during their productive years, is both equitable and practicable. It offers security in advancing years against misfortunes which often necessitate the relinquishment of one's most cherished professional memberships because of the burden of dues. All Life Membership fees are added to the Endowment Fund of the College, and thus contribute to the security of the College as well as to the security of its members. To date, January 31, 1940, 128 physicians have become Life Members. Life Membership fees may be deducted on income tax returns.

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### GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of a gift of the 3rd edition, "Pharmacology, Materia Medica and Therapeutics," by the author, Dr. Charles Solomon (Associate), Brooklyn, N. Y.

Donations of books by members of the College have resulted in the building up of a most interesting and worthwhile Library of books dealing primarily with Internal Medicine and its allied specialties. These books serve a definitely useful purpose.

The following donations of reprints are also acknowledged since the last report:

Dr. Maurice J. Abrams (Associate), Brewton, Ala.—1 reprint;  
 Dr. J. Edward Berk (Associate), Philadelphia, Pa.—5 reprints;  
 Dr. George Warren Burnett (Associate), Baltimore, Md.—2 reprints;  
 Dr. Joseph F. Elward (Associate), Washington, D. C.—3 reprints;  
 Dr. J. O. Finney (Associate), Gadsden, Ala.—2 reprints;  
 Dr. Jacob C. Geiger, F.A.C.P., San Francisco, Calif.—19 reprints;  
 Dr. Glenville Giddings, F.A.C.P., Atlanta, Ga.—1 reprint;  
 Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;  
 Dr. Crawford R. Green, F.A.C.P., Troy, N. Y.—1 reprint;  
 Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—9th, Second Series, Supplement to "Modern Drug Encyclopedia and Therapeutic Guide";  
 Dr. Hartwell Joiner, F.A.C.P., Gainesville, Ga.—1 reprint;  
 Dr. David W. Kramer, F.A.C.P., Philadelphia, Pa.—6 reprints;  
 Dr. A. B. McCreary (Associate), Jacksonville, Fla.—1 reprint;  
 Dr. Samuel Weiss, F.A.C.P., New York, N. Y.—2 reprints.

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#### REGIONAL MEETING OF EASTERN PENNSYLVANIA MEMBERS

Under the Governorship of Dr. Edward L. Bortz, Fellows and Associates of the College residing in eastern Pennsylvania held their second annual "Round-Up" at Philadelphia, February 9, 1940. A buffet luncheon was served at the College Home, 4200 Pine St., followed by a scientific program at the Medical Laboratories of the University of Pennsylvania.

1. "Clinical Uses of Intestinal Intubation," Dr. W. Osler Abbott, Philadelphia.
2. "Non-Hypoglycemic Coma Incident to Insulin Treatment of Schizophrenia," Dr. Kenneth Appel and Dr. Lauren H. Smith, Philadelphia.
3. "The Prognostic Value of the Electrocardiogram," Dr. Jesse Lenker, Harrisburg.
4. "Gastrosocopy," Dr. Louis Clerf, Philadelphia.
5. "Management of Hyperthyroidism," Dr. Stanley Conklin, Sayre.
6. "Vitamin Accomplishments," Dr. John Willard, Philadelphia.

In the evening a dinner was given at the Penn Athletic Club, where Dr. Harry B. Wilmer, F.A.C.P., and members of the Philadelphia Orpheus Club provided entertainment. Among those who addressed the dinner meeting were Dr. William D. Stroud, Treasurer; Dr. O. H. Perry Pepper, President; and Mr. E. R. Loveland, Executive Secretary.

There was a large and representative attendance of the College members from eastern Pennsylvania, with a number of the Governors of the College from neighboring states also present as guests.

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Dr. Graham Asher, F.A.C.P., Kansas City, Mo., recently was awarded first prize for the best scientific exhibit at the annual meeting of the Southern Medical Association. His exhibit was of a machine which visualizes the beating of the human heart on a fluorescent screen, keeping it visible for at least fifteen seconds. It is said



that heart conditions can be diagnosed by watching this record. The fluorescent film may be kept as a permanent record.

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Major General Charles R. Reynolds, F.A.C.P., retired Surgeon General of the U. S. Army, has accepted an appointment as Director of the newly created Bureau of Tuberculosis Control for the State of Pennsylvania and has his headquarters at Harrisburg. Among members of an advisory committee appear the names of Dr. Burgess Gordon, F.A.C.P., Philadelphia; Dr. Robert G. Torrey, F.A.C.P., Philadelphia; Dr. Charles Howard Marcy, F.A.C.P., Pittsburgh; Dr. Charles H. Miner, F.A.C.P., Wilkes-Barre; and Dr. William Devitt, F.A.C.P., Allenwood.

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#### AMERICAN PHYSICIANS ART ASSOCIATION

The annual exhibit of the American Physicians Art Association will be held at the Belmont-Plaza Hotel, New York City, June 9-15, at the same time as the annual session of the American Medical Association. The entire top floor of the hotel will be utilized by the Physicians Art Association. The New York Physicians Art Club will act as hosts. Details of the exhibit plans may be obtained from Dr. Abraham Wolbarst, 114 East 61st Street, New York City, or from the President, Dr. Henry N. Moeller, 327 Central Park West, New York City.

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Six members of the editorial board of the North Carolina Medical Journal are Fellows of the American College of Physicians:

Dr. Paul P. McCain (Chairman), Sanatorium;  
Dr. W. Reece Berryhill, Chapel Hill;  
Dr. C. C. Carpenter, Wake Forest;  
Dr. Frederic M. Hanes, Durham;  
Dr. Paul H. Ringer, Asheville;  
Dr. Wingate M. Johnson (Editor), Winston-Salem.

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Dr. Otis G. King (Associate), Bluefield, W. Va., is President of the Mercer County (West Virginia) Medical Society for the current year.

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The North Carolina Neurological and Psychiatric Association held its annual meeting at Charlotte, N. C., January 26, 1940. Dr. Mark Griffin, F.A.C.P., Asheville, is Vice President of the organization and Dr. Archie A. Barron, F.A.C.P., Charlotte, was the program chairman. Dr. Barron led a round table discussion on "Acute Infectious and Suppurative Conditions of the Brain and Spinal Cord—Sulfanilamide, etc."; Dr. Kenneth E. Appel, F.A.C.P., Professor of Psychiatry at the University of Pennsylvania, Philadelphia, presented a paper on "Frontiers in Psychological Medicine"; and Dr. Mark Griffin, F.A.C.P., Asheville, was one of those who discussed a paper on "Neurological Heredity in North Carolina."

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At the Methodist Hospital of Brooklyn, N. Y., Dr. Frank Bethel Cross, F.A.C.P., has been appointed Chief Attending Physician; Dr. Alexis T. Mays, F.A.C.P., Senior Attending Physician; and Dr. Irving L. Cabot, F.A.C.P., Attending Physician.

Dr. Ira A. Darling, F.A.C.P., resigned as Superintendent of the Springfield State Hospital (Sykesville, Md.) January 14, 1940, to accept the position of Superintendent of the Torrance State Hospital (Torrance, Pa.), January 15, 1940.

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Dr. Francis R. Dieuaide, F.A.C.P., for some time Professor of Medicine and Head of the Department of Medicine at Peiping Union Medical College, Peiping, China, has accepted an appointment as of January 1, 1940, as Associate Professor of Medicine in Harvard University Medical School and Physician to the Massachusetts General Hospital.

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Dr. David W. Kramer, F.A.C.P., Philadelphia, Pa., was recently appointed Visiting Physician to the Medical Division of the Philadelphia General Hospital and Assistant Physician on Medical Services A and B of the Jefferson Hospital.

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The Resident and Consulting Staff of the City Sanitarium of St. Louis recently elected Dr. J. R. Nakada, F.A.C.P., as President of the Staff for 1940. Dr. Nakada acted as Vice President during 1939. He has also been elevated to the Staff of Consulting Internists of Missouri Baptist Hospital.

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Dr. James L. Wade (Associate) Parkersburg, W. Va., was recently elected President of the Academy of Medicine of Parkersburg.

Dr. Wade addressed the Presidents' and Secretaries' Conference of the State Medical Association in Charleston, January 6, on "Development of Public Relations by County Medical Societies."

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The sixth annual meeting of the Mississippi Valley Medical Society will be held at Rock Island, Ill., September 25 to 27, 1940. The meeting will consist largely of practical instruction courses. Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., is the Secretary-Treasurer. Among the Society's Board of Directors are Dr. Nathan S. Davis, III, F.A.C.P., Chicago; Dr. F. G. Norbury, F.A.C.P., Jacksonville; and Dr. D. G. Stine, F.A.C.P., Columbia.

Dr. James G. Carr, F.A.C.P., Chicago, Secretary and Professor of Medicine, Northwestern University School of Medicine, was the 1939 recipient of the Distinguished Service Award of the Mississippi Valley Medical Society, "in recognition of his innate sincerity, his deep understanding of medical problems, his kindly ministrations, with a fine basic personality."

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Western Reserve University School of Medicine recently announced a grant of \$6,000 by the John and Mary R. Markle Foundation, in continuation of investigations on methods of revascularizing the heart after coronary obstruction.

The University also announces a grant of \$1,250 from the National Research Council to support from January 1 to June 30, 1940, a study of human ovulation under the direction of Dr. William W. Greulich, Professor of Physical Anthropology and Anatomy and Director of the Brush Foundation.

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The American Association for the Study of Goiter again offers the Van Meter Prize Award of \$300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association, which will be held at Rochester, Minn., on April 15, 16 and 17, provided essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a type-written, double spaced copy sent to the Corresponding Secretary, Dr. W. Blair Mosser, 133 Biddle St., Kane, Pa., not later than March 15.

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Dr. William W. Cadbury, F.A.C.P., Superintendent of the Canton (China) Hospital, is Chairman of the Executive Committee of the Canton International Red Cross. This organization has 43 stations where food or medical relief is given to refugees and sufferers. Among the activities listed in its latest report are:

- Over 4000 refugees in four camps;
- Over 70,000 meals served every week from 28 feeding centers;
- Over 10,000 dispensary treatments weekly;
- Nearly 50,000 quinine pills given out in the last month;
- Medical supplies distributed freely to hospitals in the city and to 24 towns and villages outside;
- Doctors procured for needy places;
- General Medical Service to civilian population and to refugee camps;
- 30,000 inoculations for cholera and many smallpox vaccinations;
- Assistance rendered to four orphanages;
- 5,000 inmates of Government institutions assisted.

Dr. Cadbury recently returned on leave to Moorestown, N. J.

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Dr. O. Costa Mandry, F.A.C.P., San Juan, is Chairman of the Editorial Board of the Puerto Rico Health Bulletin, which is edited and published by the Insular Department of Health.

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The thirty-sixth Annual Congress on Medical Education and Licensure was held at Chicago, February 12 and 13, 1940. Dr. John H. Musser, F.A.C.P., New Orleans, presided at one of the afternoon sessions, at which Dr. Nathan B. Van Etten, F.A.C.P., President-Elect of the American Medical Association, New York City, presented a paper on "Program for the Instruction of Interns," and Rear Admiral Ross T. McIntire, Surgeon General of the U. S. Navy, Washington, D. C., presented a paper on "Medical Education in Relation to the Naval Service."

Dr. Alan Brown, F.A.C.P., Professor of Pediatrics on the University of Toronto Faculty of Medicine, presented a paper on "The Rôle That a Children's Hospital Should Play in the Community."

The Federation of State Medical Boards was addressed by Dr. Van Etten and formal papers were presented by the following:

- Dr. Joseph H. Pratt, F.A.C.P., Boston, "The Refugee Physician";
- Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa, "Inter-American Relation in Medical Education and Licensure";
- Dr. Willard C. Rappleye, F.A.C.P., New York City, "Advisory Council on Medical Education as Related to Licensure."

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Dr. Nathan B. Van Etten, F.A.C.P., New York City, spoke on "Medical Care and the Medical Profession" January 9 in connection with the De Lamar Foundation of the Johns Hopkins University School of Hygiene and Public Health at Baltimore.

Dr. J. Murray Kinsman, F.A.C.P., Louisville, Ky., recently addressed the Evanston Branch of the Chicago Medical Society on "Present Status of Sulfapyridine."

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Dr. William B. Castle, F.A.C.P., Professor of Medicine, Harvard University Medical School, Boston, was awarded the Walter Reed Medal at a meeting of the American Society of Tropical Medicine in Memphis, Tenn., November 21. The citation states that the award was made in consideration of his "meritorious achievements in the field of tropical medicine, his outstanding leadership and scientific investigations which have resulted in most important additions to our knowledge of sprue and related anemias." The award is given only in years when there has been particularly outstanding work. The medal had not been awarded during the past four years.

Dr. Castle was awarded the John Phillips Medal of the American College of Physicians for 1933.

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It was recently announced that Dr. Martin A. Mortensen, F.A.C.P., Santa Monica, Calif., would return as a member of the staff in internal medicine of the Battle Creek Sanitarium, Battle Creek, Mich.

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Dr. Burton R. Corbus, F.A.C.P., Grand Rapids, President of the Michigan State Medical Society, addressed the Wayne County Medical Society at Detroit on December 4 on "The Function of the State Medical Society."

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Dr. Soma Weiss, F.A.C.P., Hersey Professor of the Theory and Practice of Physics at Harvard University Medical School, is Chairman, and Dr. Sidney Burwell, F.A.C.P., Dean of the Medical School, and Dr. William B. Castle, F.A.C.P., Professor of Medicine, are ex officio members of a committee on pharmacotherapy recently established at Harvard University to develop research and improve graduate training in the field of pharmacology and experimental therapeutics, coördinating the efforts of practicing physicians and Harvard scientists in biology, chemistry and medicine. It is said that a group of corporations interested in medical and therapeutic research will supply the funds to support the work of the committee for the next five years.

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Dr. Walter Baumgarten, F.A.C.P., St. Louis, has been elected Editor of the Journal of the Missouri State Medical Association.

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The November-December issue of the Review of Gastroenterology was dedicated to Dr. Anthony Bassler, F.A.C.P., New York, in honor of his sixty-fifth birthday. For the past four years Dr. Bassler has been President of the National Gastroenterological Association. He is the author of several books in his specialty and has made many contributions to medical journals. At present he is consulting gastro-enterologist to several hospitals in New York City and environs.

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Dr. Maxwell Finland, F.A.C.P., Boston, addressed the Cincinnati Academy of Medicine December 5 on "Serotherapy and Chemotherapy of Pneumonia."

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Dr. Wallace M. Yater, F.A.C.P., College Governor for the District of Columbia, Washington, D. C., addressed a joint meeting of the Medical Society of the District

of Columbia and the Baltimore City Medical Society December 1 in Baltimore on "Pathogenesis and Prognosis of Bundle Branch Block."

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Dr. Raymond Hussey, F.A.C.P., Baltimore, has been appointed chairman of a state medical board for occupational diseases by the Governor of Maryland.

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Among lecturers in a series of free public meetings on medical subjects, which began January 7 at Harvard University Medical School, were the following:

Dr. Chester M. Jones, F.A.C.P., January 7, "Digestion and Indigestion";  
Dr. Chester S. Keefer, F.A.C.P., January 21, "What About Sulfanilamide?";  
Dr. Paul D. White, F.A.C.P., February 4, "Facts and Fancies About Heart Disease";  
Dr. William B. Breed, F.A.C.P., March 10, "Health in Middle Age."

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Dr. David M. Cowie, F.A.C.P., Ann Arbor, has been reelected Secretary of the Michigan Pediatric and Infectious Disease Society.

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Dr. Priscilla White, F.A.C.P., Boston, addressed the Camden County (N. J.) Medical Society at Camden, N. J., December 5, on the subject of diabetes.

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Dr. William H. Ross, F.A.C.P., Brentwood, was honored recently by the Suffolk County (N. Y.) Medical Society at a dinner in recognition of his fifty years of medical practice. Among those who offered tributes to Dr. Ross was Dr. Peter Irving, F.A.C.P., New York, Secretary of the New York State Medical Society. Dr. Ross, now seventy-seven years of age, was formerly president of the state medical society, the Associated Physicians of Long Island, the Suffolk County Medical Society and the New York Association of Superintendents and Managers of Tuberculosis Sanatoria.

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Dr. Bayard T. Horton, F.A.C.P., Rochester, Minn., addressed the New York Academy of Medicine December 7 on "Clinical Aspects with Respect to the Venous System."

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Dr. Edwin C. Swift, F.A.C.P., and Dr. Arthur J. Logie (Associate), both of Jacksonville, Fla., were recently elected Vice Presidents of the Florida East Coast Medical Association.

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Dr. Hugh R. Butt (Associate), Rochester, Minn., addressed the North Shore Branch of the Chicago Medical Society January 2 on "Vitamins, Recent Advances and Their Clinical Application."

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Dr. Emanuel Libman, F.A.C.P., New York City, delivered the fifth annual Martland Lecture before the Essex County (N. J.) Anatomical and Pathological Society, Newark, January 24, on "Endocarditis."

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Dr. Alvan L. Barach, F.A.C.P., New York City, addressed the International Spanish Speaking Association of Physicians, Dentists and Pharmacists during December on "Modern Treatment of Asthma."

Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., participated in a symposium on "Chemotherapy Including Sulfapyridine and Allied Compounds" at the annual meeting of the New York Academy of Medicine January 4.

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Dr. Albert B. McCreary (Associate), Jacksonville, State Health Officer for Florida, was recently elected President of the Florida Public Health Association.

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It was recently announced that Dr. Walter H. Baer (Associate), formerly Superintendent of the Peoria (Ill.) State Hospital, has been appointed Acting Superintendent of the Manteno (Ill.) State Hospital.

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Dr. Henry H. Turner, F.A.C.P., Oklahoma City, addressed the Golden Belt Medical Society, Salina, Kan., January 4, on "Endocrinology in General Practice."

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Dr. David W. Gillick, F.A.C.P., Superintendent and Physician-in-Charge of the Shawnee (Okla.) Indian Sanatorium, has been appointed Medical Director for District No. 5 of the Indian Medical Service.

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Dr. Orville E. Egbert, F.A.C.P., El Paso, Tex., was recently installed as President of the Southwestern Medical Association.

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Dr. Roscoe L. Sensenich, F.A.C.P., South Bend, Ind., Dr. Henry R. Carstens, F.A.C.P., Detroit, and Dr. Hilton S. Read, F.A.C.P., Atlantic City, N. J., were speakers at the fourteenth annual meeting of the National Conference on Medical Service held at Chicago February 11.

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Dr. James F. McFadden, F.A.C.P., and Dr. John Zahorsky, F.A.C.P., were among members of the Faculty of St. Louis University School of Medicine who were recently honored at a dinner sponsored by the Women's Club of the School of Medicine. The dinner was given in recognition of all of those who had served 25 years on the Faculty. Replicas of the seal of the university were presented to each guest of honor.

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Dr. Cornelius P. Rhoads, F.A.C.P., New York City, addressed the New York Pathological Society January 25 on "Aplastic Anemia."

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Dr. Martha Tracy, F.A.C.P., Dean of the Woman's Medical College of Pennsylvania, has been made Assistant Director of Public Health of Philadelphia. She will continue as Dean of the Medical College until the end of the present academic year or until a successor is elected.

Dr. Tracy received her medical degree from the Woman's Medical College of Pennsylvania in 1904 and the degree of doctor of public hygiene from the University of Pennsylvania in 1917. She has been associated with the Woman's Medical College since 1913, first as Professor of Physiologic Chemistry (1913-21), then as Professor of Hygiene (1921-23), then as Professor of Preventive Medicine (1923-31) and as Dean since 1918. She has been a member of the Philadelphia Board of Health since 1936.

Dr. Oscar Lotz, F.A.C.P., Milwaukee, has been elected Executive Secretary of the Wisconsin Anti-Tuberculosis Association.

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The American Social Hygiene Association held its twenty-seventh annual meeting at Chicago, February 1-2. Among speakers were Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service; Dr. Waller S. Leathers, F.A.C.P., Nashville, Tenn., "Adequacy of Preparation—Are We Giving Physicians the Training and Technics They Need?"; and Dr. Rock Sleyster, F.A.C.P., President of the American Medical Association, Wauwatosa, Wis., "Rôle of the Private Physician—How Can He Strengthen the Control Program?"

Major General Merritte W. Ireland, F.A.C.P., former Surgeon General of the U. S. Army, was awarded the William Freeman Snow Medal on behalf of the Association.

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The midwinter postgraduate clinics of the Colorado State Medical Society were held at Denver, February 7 to 9. Among guest speakers was Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, "Present Status of Our Knowledge Concerning the Treatment of the Anemias."

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Among guest speakers on the program of the third annual Atlanta Graduate Medical Assembly, January 15, under the auspices of the Fulton County (Ga.) Medical Society, the following were included:

Dr. William E. Chamberlain, F.A.C.P., Philadelphia, "Pitfalls in X-Ray Diagnosis"; Dr. Philip S. Hench, F.A.C.P., Rochester, Minn., "Chronic Infectious (Atrophic) Arthritis; Its Diagnosis and Treatment"; Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, "The Prognosis and Treatment of Hypertension."

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At the Indiana State Medical Association's annual conference of secretaries of county medical societies, held at Indianapolis, January 21, Dr. Henry H. Turner, F.A.C.P., Oklahoma City, spoke on "Postgraduate Medical Education in Oklahoma," and Dr. Peter Irving, F.A.C.P., New York City, spoke on "Hospital Insurance and Medical Indemnity."

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Dr. George R. Minot, F.A.C.P., Professor of Medicine, Harvard University Medical School, Boston, was awarded the Gordon Wilson Medal of the American Clinical and Climatological Association at its last meeting.

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Dr. J. Arthur Myers, F.A.C.P., Professor of Medicine, Preventive Medicine and Public Health at the University of Minnesota Medical School, Minneapolis received the 1939 gold medal of the Society of Puerto Rican Tuberculosis Physicians for "outstanding work in the field of Tuberculosis." Dr. Myers addressed the annual session of the Puerto Rico Medical Association and gave a series of lectures under the auspices of the Society of Puerto Rican Tuberculosis Physicians during December, 1939.

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Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn., has succeeded Dr. Moses Barron, F.A.C.P., Minneapolis, Minn., as President of the Minnesota Society of Internal Medicine.

Dr. Grant Thorburn, F.A.C.P., New York City, delivered an address on tuberculosis February 6 before the Essex County (N. J.) Medical Society at Newark.

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Dr. Robert F. Loeb, F.A.C.P., New York City, is Chairman of the Committee, and Dr. I. Ogden Woodruff, F.A.C.P., New York City, is a member, appointed by Dr. S. S. Goldwater, Commissioner of Hospitals of New York City, to assist in the selection of a medical staff for the new five-hundred bed hospital for tuberculosis soon to be completed. Applicants for appointments must be citizens of the United States and must be licensed to practice in New York. The superintendent, roentgenologist and pathologist will be appointed from civil service lists.

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Dr. John H. Skavlem, F.A.C.P., Cincinnati, has been appointed Acting Medical Director of the Hamilton County (Ohio) Tuberculosis Sanatorium, following the resignation of Dr. Kennon Dunham, F.A.C.P., Cincinnati, who has been associated with the Sanatorium since 1910.

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At the December meeting of the American Association for the Advancement of Science, Dr. Edmund Jacobson, F.A.C.P., announced a new instrument—The Integrating Neurovoltmeter—to afford the direct measurement of nervous or of muscular states in various diseases, without anesthetic.

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On October 24, 1939, a meeting was held at the St. Louis Medical Society in honor of Dr. William Washington Graves, Professor of Neuropsychiatry, St. Louis University School of Medicine. At this meeting, Dr. Graves was awarded a Certificate of Merit and a Gold Medal for scientific accomplishment in his classification of scapulae and other inherited characters, and of his discovery of "The Age-Incidence Principles of Investigation."

The St. Louis Medical Society has given this Certificate of Merit for scientific accomplishment on only two occasions before Dr. Graves received it.

The first was given to Dr. Evarts A. Graham and his associates, Drs. Glover H. Copher, Warren H. Cole and Sherwood Moore, June 7, 1927, for their work in cholecystography. The second was given to Dr. Edward A. Doisy, March 19, 1935, for his achievements in hormone chemistry and physiology.

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During the twentieth annual meeting of the American Student Health Association at the Hotel New Yorker, New York, December 28 and 29, 1939, a luncheon session was devoted to the subject of tuberculosis among college and university students. Presiding was Dr. Kendall Emerson, managing director of the National Tuberculosis Association. Fellows of the College who took part in the meeting included Dr. J. Burns Amberson, Jr., Professor of Medicine, Columbia University, who spoke on "Dividends from a Tuberculosis Control Project among Students"; Dr. Herbert R. Edwards, director of the Bureau of Tuberculosis, New York City Department of Health, who discussed the paper; and Dr. Charles E. Lyght, director of the Student Health Service, Carleton College, Northfield, Minnesota, who presented the ninth annual Report of the Tuberculosis Committee.



## OBITUARIES

## DR. CHARLES ANDREW RAY

Dr. Charles Andrew Ray, F.A.C.P., Charleston, W. Va., died January 21, 1940, of a heart attack.

Dr. Ray was born in Charleston, W. Va., May 14, 1864, and received his early education in the public schools and high school of Milton, W. Va. He received his degree of Doctor of Medicine from the College of Physicians and Surgeons (Baltimore) in 1887 and served his internship at the Baltimore City Hospital. Later, he took postgraduate work at Johns Hopkins University School of Medicine and at the New York Polyclinic Medical School and Hospital. In 1917, he began the practice of medicine in Charleston.

Dr. Ray was a member of the Kanawha County Medical Society, serving as President in 1925; the West Virginia State Medical Association, serving as President in 1928; the Tri-State Medical Society, the Southern Medical Association, the American Medical Association and a Fellow of the American College of Physicians since 1926. He was Editor-in-Chief of the West Virginia Medical Journal in 1927 and continued to serve as Associate Editor of this Journal until 1938. He was Chief of the Medical Staff and Instructor to the Nurses Training School of the Kanawha Valley Hospital and President of the County Court of Kanawha County at the time of his death.

"As a man of unfaltering courage, of understanding and of rare good humor, Dr. Ray exemplified all of the finest attributes of a noble profession."

ALBERT H. HOGE, M.D., F.A.C.P.

Governor for West Virginia

## DR. ALBERT W. NELSON

Albert William Nelson was born in Owatonna, Minn., January 20, 1878, and died in a local hospital in Battle Creek of a stroke of apoplexy January 5, 1940. His family moved to Battle Creek during his boyhood and he attended Battle Creek College, obtaining his B.S. degree in 1898. After four years' training he graduated with his M.D. from the American Medical Missionary College in 1903 and at once joined the Sanitarium Medical Staff with which he served until 1920, when he entered private practice and at the same time was on the medical staff of the Maple Street Hospital until it closed in 1930. Dr. Nelson was a Fellow of the American College of Physicians and Member of the Calhoun County and State Medical Society and a Fellow of the American Medical Association. Soon after his graduation the doctor spent some time doing postgraduate work in Baltimore. In 1936 he did postgraduate work at Washington University School of Medicine in St. Louis, in 1937 Cook County Hospital, Chicago, and in 1938 the

University of Buffalo School of Medicine, these courses running from two to three weeks. He was a quiet, dignified Christian gentleman and always enjoyed an excellent practice. Dr. Nelson's medical work was also his mission and hobby and he never failed to answer a call with no thought of whether there would be a fee. His first apoplectic stroke was on June 3, 1939, which was comparatively light and from which he slowly made a very fair recovery and was able for several months to attend his office and see patients daily. He did not recover consciousness from the final stroke and passed on within a few hours. He was unmarried and left behind a sister, Miss Mable Nelson, and two paternal aunts and one uncle, too far distant to attend the funeral which was crowded with friends and former patients.

A. B. OLSEN, M.D., F.A.C.P.,  
Battle Creek, Michigan

### DR. MARTIN LUTHER STEVENS

Dr. Martin L. Stevens was born in Thornville, Ohio in 1864. He graduated in medicine from the University of Maryland (Baltimore Medical College) in 1891. After several years in general practice, Dr. Stevens joined the staff of the Winyah Sanatorium in Asheville, remaining in association there until 1901, when he established himself in private practice. He limited his work to internal medicine, specializing in tuberculosis, and was active in it until his sudden death, while dressing, on the morning of January 20, 1940, apparently from a coronary occlusion.

Dr. Stevens' interest in medical societies was continuous throughout his career. He was senior honorary member of the Buncombe County Medical Society, a Fellow of the North Carolina State Medical Society (President, in 1932), a member and past President of the North Carolina Board of Medical Examiners, charter member of the National Tuberculosis Association, as well as a member of the North Carolina State Tuberculosis Association, the Southern Tuberculosis Conference, and a corresponding member of the International Tuberculosis Conference, as well as a member of the American Clinical and Climatological Association, the Southern Medical Association, and of the American Medical Association, being a member of the House of Delegates from 1924 until his death. He became a Fellow of the American College of Physicians in 1929, and was a diplomate of the American Board of Internal Medicine.

Dr. Stevens was a loyal and constant attendant at medical meetings, but by reason of his modest and retiring disposition rarely participated on the floor in discussions. In his earlier years, however, he was the author of quite a few articles on tuberculosis. During the World War, he was Chairman of the Medical Advisory Board, having supervision of the western counties of the state.

He was a devoted, active member of St. Mark's Lutheran Church of Asheville, as well as a member of the National Council of his church, and a

member of the Rotary Club. He was a member of the staffs of various tuberculosis sanatoria and hospitals of the city, being Chief of Staff of St. Joseph Hospital in 1939. He was a member of the Board of Directors of the Western Carolina Tuberculosis Sanatorium, which institution he visited only a few hours previous to his death.

Dr. Stevens left no children, but he is survived by his widow, Mrs. Lula Mary Patterson Stevens, whom he married in 1894.

In spite of an unusual degree of modesty and a very retiring disposition, Dr. Stevens was signally honored by his colleagues with positions of honor and trust, all of which he discharged with fidelity and sincerity. He maintained his interest, as well as failing strength of later years permitted, in all medical societies and felt a keen interest in the American College of Physicians, whose meetings he attended whenever possible. In his passing, the medical profession of his community and state, as well as a larger sphere of friends and acquaintances reached through his broad reputation, will miss a faithful, loyal and fine friend.

C. H. COCKE, M.D., F.A.C.P.,  
Governor for North Carolina

#### DR. JOHN CONOVER CLAYTON

John Conover Clayton, F.A.C.P., Freehold, N. J., died of coronary thrombosis on November 25, 1939, at the Princeton Hospital. He was born at Princeton, N. J., February 25, 1882, where his early life was spent, and from which place he went to Lawrenceville School, whence he was graduated in 1901. He spent the next two years in Princeton University, and then matriculated at the University of Pennsylvania School of Medicine, being graduated in 1907. The next two years were passed in internships at the Naval Hospital, Washington, D. C., and the Manhattan State Hospital, New York, N. Y.

In 1909, Dr. Clayton began general practice in Freehold, N. J., where he lived and carried on his profession until his death. He became especially interested in circulatory diseases, and, at the age of 38, began post-graduate work in cardiology at the New York Post-Graduate Medical School and Hospital, where he continued for two years. He became the Attending Cardiologist at the Fitkin Memorial Hospital, Neptune, N. J., and at the Riverview Hospital, Red Bank, N. J. He was, at one period, Attending Physician to the Ann May Hospital at Spring Lake, N. J.

Dr. Clayton was a past President and Secretary of the Monmouth County Medical Society, a member of the Medical Society of New Jersey, Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1931.

Beside being a leader in his profession, Dr. Clayton took an active interest in both church and civic affairs. His chief hobbies were golf and

football, and it was at the Navy game at Princeton that he suffered the illness of which he died a few hours later in the Princeton Hospital.

GEORGE H. LATHROPE, M.D., F.A.C.P.,  
Governor for New Jersey

### DR. CHARLES WALTER STONE

On December 9, 1939, Dr. Charles Walter Stone, F.A.C.P., died at Cleveland, Ohio, after an illness of more than a year.

Born in Pittsburgh, Pa., in 1879, he attended school in that city and was graduated from Washington and Jefferson College with the degree of A.B. He studied medicine at Johns Hopkins University and received his degree of Doctor of Medicine in 1905. He served as intern on the Medical Service at the Lakeside Hospital in Cleveland from 1905 to 1906. After this, Dr. Stone became resident in medicine at Lakeside Hospital under Dr. C. F. Hoover and Dr. E. F. Cushing. Following his years of resident service at Lakeside Hospital, Dr. Stone studied in France, Germany, and England. His postgraduate studies were entirely in Neurology and Psychiatry. Then he returned to Cleveland and entered the practice of Neurology and Psychiatry. He became one of the outstanding specialists in Neuro-Psychiatry in Cleveland.

Always interested in the academic angle of his chosen specialty, he held numerous leading posts in the Medical Department of Western Reserve University, eventually filling the post of Associate Clinical Professor of Nervous and Mental Diseases. He organized the Observation Department for Nervous and Mental Diseases at the City Hospital of Cleveland, and also at Lakeside Hospital.

Dr. Stone was interested always in military affairs. As a member of the National Guard of Ohio, he saw duty with the 112th Engineers during the Dayton Flood and with the same organization Dr. Stone served on the Mexican border and later saw service with the 37th Division, Ohio N. T., in France, from which organization he was drafted for special service in the Neuro-Psychiatric Department of the American Expeditionary Forces, under the late Col. Thomas W. Salmon.

Throughout his extremely active life Dr. Stone interested himself in the furtherance of the aims and ideals of organized medicine. Locally, he was active in the Academy of Medicine of Cleveland and was President of that organization in 1926. He served the Ohio State Medical Association in many important committee assignments, as member of the House of Delegates and later as President. To the American Medical Association he served as member of the House of Delegates for many years. His service has further been freely given to the Cleveland Medical Library Association from the years 1929 through 1938.

Dr. Stone was a member of all his local medical organizations, in addi-

tion to which he has been a Fellow of the American College of Physicians since 1920, and a life member of the College since 1937. He was a member of the American Psychiatric Association and of many local medical and fraternal organizations.

An intense worker, a strong supporter of the aims of organized medicine, an inspiring teacher, a deep student, a kindly gentleman, beloved by his friends and by his patients, his memory is cherished and his loss condoned by friends, colleagues, and patients alike. His life was one of complete service. He never swerved from the duties of public or private service, no matter how difficult the task.

RICHARD DEXTER, M.D., F.A.C.P.  
Cleveland, Ohio

### DR. ORAN IDNIRE CUTLER

Dr. Oran Idnire Cutler (Associate) died September 15, 1939, at 39 years of age. His untimely death was the result of an automobile accident which occurred as he was returning from a meeting of the Los Angeles Pathological Society.

He was born December 25, 1899, at Swedesburg, Iowa. He received his B.S. degree from Union College (Nebraska) and his M.D. degree from the College of Medical Evangelists in 1924. His intern year was served at the Santa Tomas Hospital, Panama, Canal Zone. He was awarded a fellowship in Pathology by the National Research Council and served one year, 1926-27, under Dr. William Ophüls at Stanford University, and a second year under Dr. H. Gideon Wells at the University of Chicago; he returned to Chicago to serve as instructor in Dr. Wells' department during the summer of 1932. With the exception of this period at Chicago, he served continuously in the Pathology Department of his Alma Mater, the College of Medical Evangelists, Loma Linda and Los Angeles, California, from 1928 to the time of his death, as Instructor, Assistant Professor, Associate Professor, and Professor of Pathology. He was a member of the American Association of Pathologists and Bacteriologists, the American Society of Clinical Pathologists, and the Los Angeles Pathological Society, as well as his county and state medical societies and the American Medical Association. He was a continuous participant in the activities of these various societies. He served as pathologist to the Los Angeles County Hospital, the San Bernardino County Hospital, and the Riverside County Hospital, also as Coroner's Physician in San Bernardino County.

His loss is keenly felt by all who have been associated with him in these activities. His scientific interest and integrity were of the highest order and all who came in contact with him felt his stimulus. His prime activities were those of his pathology teaching. As a teacher, he had few peers. His passing has been an irreparable loss to his students, his medical school, his

teaching and professional fellows, and to all who learned to trust him and depend upon him.

NEWTON EVANS, M.D., F.A.C.P.,  
Los Angeles, Calif.

### DR. WILLIAM BURR SOPER

Dr. William Burr Soper, medical director of the William Wirt Winchester Hospital, tuberculosis unit of the New Haven Hospital, and associate professor of medicine in the Yale University School of Medicine, died in New Haven Hospital on October 30, 1939 of brain tumor.

Dr. Soper was born at Bloomington, Ill., Dec. 28, 1882. He was graduated from Yale University in 1904, and received his medical degree from Columbia University College of Physicians and Surgeons in 1908. While an undergraduate at Yale he was secretary of the Freshman Navy, and played on the varsity football team. He was also a member of the banjo and mandolin club, Psi Upsilon, and Skull and Bones.

After receiving his medical degree Dr. Soper was an intern, 1909-11, at Presbyterian Hospital, New York City, and Bacteriologist and Serologist, 1911-13. In 1913-14 he took postgraduate work in pathology at the University of Freiburg, Germany. In 1914 he became engaged in tuberculosis work at Saranac Lake, N. Y. He remained there until 1917 when he was commissioned Captain in the United States Medical Corps, being assigned to Base Hospital No. 2, the Presbyterian Hospital Unit from New York that went overseas immediately after being organized. The unit was assigned to the British Expeditionary forces, taking over a hospital in Etretet, France. Dr. Soper was made Commanding Officer of the Unit in 1918, and in the same year was promoted to rank of Major.

Upon his return to the United States in 1919 he joined the Rockefeller Foundation, engaged in work for the prevention of tuberculosis in France. At the close of this work in September, 1921, he returned to Saranac Lake where he remained until appointed the first director of the Bureau of Tuberculosis of the New Haven Department of Health in 1926. The following year, after the William Wirt Winchester Hospital was restored to civilian use, Dr. Soper became its medical director, in which position he was serving at the time of his death. Coincident with this appointment he became a member of the faculty of the Yale University School of Medicine in which he held the rank of associate professor of medicine. In addition to his teaching work he served as tuberculosis consultant in the Yale Department of University Health. In 1937 Dr. Soper was appointed to the New Haven Board of Health Commissioners and he served on the medical advisory committee of the Visiting Nurse Association since 1933.

Dr. Soper was a Diplomate, American Board of Internal Medicine, member of his county and state medical societies, American Clinical and Clima-

tological Association and Interurban Clinical Club; member and former Vice President of the National Tuberculosis Association; Fellow, American Medical Association; Fellow of the American College of Physicians since 1933. He was the author of numerous medical articles including translations of scientific papers from the French, and was frequently called upon to deliver lectures on tuberculosis.

From the above it can be seen that Dr. Soper was a busy and hardworking student keenly interested in the welfare of his fellow man. His friendly and delightful personality endeared him to all with whom he came in contact, and his untimely death is mourned by his medical associates, and by hosts of others to whom he was not only physician but friend as well.

CHARLES H. TURKINGTON, M.D., F.A.C.P.,  
Governor for Connecticut

### DR. ROY GEORGE PFOTZER

The death of Dr. Roy George Pfozter occurred suddenly on August 9, 1939.

Dr. Pfozter was born in Buffalo on November 20, 1892; attended University of Buffalo, earning a degree in Chemistry; M.D., C.M., 1924 and D.P.H., 1924, Queens University, Faculty of Medicine; Intern, Buffalo City Hospital, 1924-25; Assistant Attending Physician, 1925-27, Attending Physician, 1927-30, and Associate Visiting Physician, Buffalo City Hospital; formerly Assistant Attending Physician and more recently Electrocardiographer and Attending Physician, Millard Fillmore Hospital; Associate in Medicine, University of Buffalo School of Medicine; at one time, Biochemist in the Department Laboratory of the City of Buffalo; First Lieutenant, Sanitary Corps, U. S. Army and assigned to Red Cross Work in Serbia as Sanitary Officer during the World War; Member, Academy of Medicine of Buffalo, Erie County Medical Society, New York State Medical Association, American Heart Association, Association for the Study of Internal Secretions, American Medical Association and Fellow of the American College of Physicians since 1934; Diplomate, American Board of Internal Medicine.

Dr. Pfozter practiced Internal Medicine in Buffalo and taught in the Medical School most of the time. He was very active as Attending Physician at the Millard Fillmore Hospital.

Dr. Pfozter's work was of the highest type and he was an excellent teacher, with a most exceptional foundation. He was quite active in the medical life of Buffalo and his loss is deeply regretted by the whole community.

NELSON G. RUSSELL, M.D., F.A.C.P.,  
Governor for Western New York

## DR. ARTHUR BURKE O'BRIEN

Dr. Arthur Burke O'Brien (Associate) died at Rochester, N. Y., July 6, 1939, as a result of an automobile accident. He was born at Ellicottville, N. Y., January 24, 1896. After doing his pre-medical work at Niagara University he entered the University of Buffalo School of Medicine from which he graduated in 1921. He interned at St. Mary's Hospital, 1921-22, and then engaged in the practice of general medicine in Rochester. He was appointed to the medical staff of St. Mary's Hospital in 1923 and was advanced to Senior Medical Attendant in 1928, the latter appointment held until his death.

Dr. O'Brien was a member of the Rochester Academy of Medicine, Rochester Pathological Society, Monroe County Medical Association and a Fellow of the American Medical Association. He had been an Associate of the American College of Physicians since 1939.

DAVID B. JEWETT, M.D., F.A.C.P.



PROGRAM  
TWENTY-FOURTH ANNUAL SESSION  
AMERICAN COLLEGE OF PHYSICIANS  
CLEVELAND, OHIO

April 1-5, 1940

GENERAL SESSIONS AND LECTURES

O. H. Perry Pepper, President

CLEVELAND COMMITTEE ON ARRANGEMENTS

Howard T. Karsner, General Chairman

Edward H. Cushing	E. P. McNamee
Harold Feil	V. C. Rowland
Joseph M. Hayman, Jr.	John A. Toomey

COMMITTEE ON CLINICS AND DEMONSTRATIONS

Joseph M. Hayman, Jr., Chairman

Samuel S. Berger	Harry V. Paryzek
Russell L. Haden	Robert M. Stecher
Fred C. Oldenburg	Charles T. Way

Harley A. Williams

COMMITTEE ON TRANSPORTATION

Edward H. Cushing, Chairman

McKinley London	J. C. Placak
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COMMITTEE ON ENTERTAINMENT

E. P. McNamee, Chairman

F. A. LeFevre	H. D. Piercy
J. P. Tucker	

COMMITTEE ON AUDITORIUM

John A. Toomey, Chairman

C. L. Hartsock	A. D. Nichol
R. A. Reading	

COMMITTEE ON PUBLICITY

V. C. Rowland, Chairman

H. van Y. Caldwell, Vice-chairman

Everett N. Collins	M. W. Martin
Hubert C. King	S. J. Wolpaw

COMMITTEE ON PANEL DISCUSSIONS

Harold Feil, Chairman

Frank J. Doran	Charles S. Higley
A. C. Ernstene	Roy W. Scott

Carl J. Wiggers

## WOMEN'S ENTERTAINMENT COMMITTEE

Mrs. Harley A. Williams, Chairman

Mrs. Harold Feil, Vice-chairman

Mrs. Howard T. Karsner, Vice-chairman

Mrs. William P. Garver

Mrs. Charles L. Higley

Mrs. Russell L. Haden

Mrs. Edgar P. McNamee

Mrs. William R. Hallaran

Mrs. Fred C. Oldenburg

Mrs. Charles L. Hartsock

Mrs. V. C. Rowland

Mrs. Joseph M. Hayman, Jr.

Mrs. Robert M. Stecher

Mrs. Carl J. Wiggers

## WELCOME TO CLEVELAND

A cordial welcome is extended to the Fellows and Associates of the American College of Physicians and their guests by the medical profession of the entire community, together with the Academy of Medicine of Cleveland, the Faculty of Medicine of Western Reserve University, and the members of the staffs of the various hospitals in the city. Cleveland prides itself upon the spirit of its hospitality to all visitors and this will be particularly true as concerns so distinguished an organization as the American College of Physicians. All hospitals, whether participating in the programs or not, will be glad to receive visitors who wish to study physical equipment, organization, and services of various kinds. Western Reserve University will welcome visitors to the School of Medicine and the associated hospitals, as well as to the various related professional schools.

As will be seen by reference to the program, certain hospitals and members of their staffs will actively participate in the Clinics. In addition, many of the Clinics will be conducted in part by distinguished visitors. The endeavor has been to provide a diversified and well rounded program of interest and benefit to all the members of the College. For this year at least, the usual Round Tables will be replaced by Panel Discussions. By this means, it is hoped that there will be informality and intimacy in the conferences, between those who conduct the panels and those who attend them. Each Panel is so arranged as to provide coverage of the special fields within the scope of each particular Panel. For that reason, each Panel will have from two to five distinguished physicians as leaders. The freedom of contact with these outstanding leaders should provide much in the way of information and inspiration.

The various public and private institutions of the city are deeply interested in welcoming to their halls the members of the College and their guests. In all of these, the registration badge will be sufficient for admission. The Cleveland Museum of Art represents more than a collection of objects. It is an institution which has a widespread influence in the community through lectures, demonstrations, and other activities of the modern museum. The exhibits are varied and of great interest, including art of the classical period as well as that of modern times. The Cleveland Museum of Natural History, although only recently established, has a collection now well known throughout the world. The history of the Western Reserve is characteristic of the spread of culture in the new world. The Western Reserve Historical Society occupies two buildings, one at University Circle and one on East Boulevard. The former houses a library of over 200,000 volumes, files of newspapers and an extensive genealogical file. The latter contains many objects of historical interest, including extensive Washingtoniana and the largest collection of material on Napoleon in this country. The Dunham Tavern, dating from the early nineteenth century, is open from 1 to 5 each afternoon except Monday, and contains much in the way of design, furniture and the like, to delight the hearts of those

interested in early Americana. The Garden Center, at University Circle, is open daily, except Monday, and also on Tuesday evening. An extensive horticultural library and exhibits are available, and a graduate of the Cambridge School of Landscape Architecture is in attendance.

The Cleveland Medical Library Association building is on Euclid Avenue near the University Hospitals. Beautifully designed and equipped, it houses more than 54,000 volumes and contains exhibits of great interest to the medical historian. It is open from 9:00 a.m. to 10:00 p.m. on Monday, Wednesday and Friday, and from 9:00 a.m. to 6:00 p.m. on Tuesday, Thursday and Saturday.

Information as to numerous other places well worthy of a visit will be available at the Registration Bureau.

### GENERAL INFORMATION

#### Cleveland Headquarters

Public Auditorium—General Headquarters

Hotel Statler—Hotel Headquarters

The Cleveland Public Auditorium will be general headquarters for registration, exhibits, general sessions, panel discussions and special lectures.

The Hotel Statler will be headquarters for Officers, Regents, Governors and members of the College; also headquarters for the Women's Entertainment Committee, the President's Reception and the Annual Banquet.

List of Cleveland Hotels	Blocks from Auditorium	Rates per day*	
		Single Room	Double Room
HOTEL STATLER.....	4	\$3.00-6.00	\$4.50-8.00
Allerton Hotel.....	5	2.50-2.75	4.00-4.50
Auditorium Hotel.....	$\frac{1}{2}$	2.00-2.50	3.50-6.00
Carter Hotel.....	4	3.00-5.00	4.50-8.00
Cleveland Hotel.....	3	3.00-5.00	4.50-8.00
Hollenden Hotel.....	$1\frac{1}{2}$	3.00-5.00	4.50-8.00

\* All rooms with private bath.

Members should make reservations directly with hotels of their choice. Mention the Convention of the American College of Physicians, for rates quoted are, in some instances, only for this occasion.

#### WHO MAY REGISTER—

- (a) All members of the American College of Physicians in good standing for 1940 (dues, if not paid previously, may be paid at the Registration Bureau).
- (b) All newly elected members.
- (c) Members of the Academy of Medicine of Cleveland, without registration fee, upon presentation of their 1940 membership cards.
- (d) Medical students (third and fourth years only) pursuing courses at Western Reserve University School of Medicine, without registration fee, upon presentation of matriculation cards, or other evidence of registration at this institution; exhibits, morning lectures, panel discussions and general sessions.
- (e) House Officers of the hospitals participating in the program, without registration fee, upon presentation of proper identification; exhibits, morning lectures, panel discussions and general sessions.
- (f) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.

- (g) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of \$12.00, and shall be entitled to one year's subscription to the *ANNALS OF INTERNAL MEDICINE* (in which the proceedings will be published), included within such fee.

**REGISTRATION BUREAU**—Temporary Registration Bureau will be open at the Public Auditorium on Sunday, March 31, from 2:30 to 5:00 in the afternoon, and 7:00 to 9:00 in the evening. The permanent Registration Bureau at the Auditorium will be open daily, 8:30 a.m. to 6:00 p.m., Monday to Friday, April 1-5.

**REGISTRATION BLANKS FOR ALL CLINICS, DEMONSTRATIONS AND PANEL DISCUSSIONS** will be sent to members of the College with the formal program. Guests will secure registration blanks at the Registration Bureau during the Session.

**BULLETIN BOARDS FOR SPECIAL ANNOUNCEMENTS** will be located near the Registration Bureau at the Public Auditorium, and in the lobby of the Hotel Statler.

**TRANSPORTATION**—On account of nationwide reductions in railroad fares, there are no convention rates any longer in effect. In many instances, however, reduced round trip tickets are in effect from certain localities. Physicians should consult their local ticket agents.

Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the meeting.

**Special Taxicab Rates**—The following rates will apply for all Yellow Cabs upon presentation of the Registration Badge to the driver, and include one to four passengers:

From any down town hotel to Lakeside Hospital, St. Luke's Hospital or Mt. Sinai Hospital. . . . .	\$1.00
From any down town hotel to Charity Hospital. . . . .	.35
From any down town hotel to St. Alexis Hospital, the Cleveland Clinic or City Hospital. . . . .	.75
To or from any down town hotels and the Municipal Auditorium. . .	.25

**THE GENERAL BUSINESS MEETING OF THE COLLEGE** will be held at 4:45 p.m., Thursday, April 4, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary, and the induction to office of the new President, Dr. James D. Bruce, Ann Arbor, Mich.

**BOARD AND COMMITTEE MEETINGS**—The following meetings are scheduled, as indicated. Special meetings will be announced and posted.

A *dinner meeting* of the Board of Regents and of the Board of Governors will be held at the Hotel Statler, Sunday evening, March 31, at seven o'clock.

## COMMITTEE ON CREDENTIALS

Sunday, March 31, 9:00 a.m. . . . . Public Auditorium, Executive Secretary's Office

## BOARD OF REGENTS

Public Auditorium

Sunday, March 31, 2:30 p.m.

Tuesday, April 2, 12:00 m.\*

Friday, April 5, 12:00 m.\*

## BOARD OF GOVERNORS

Public Auditorium

Monday, April 1, 5:00 p.m.

Wednesday, April 3, 12:00 m.\*

## SPECIAL FEATURES

MONDAY, APRIL 1, 1940

THE ANNUAL SMOKER will be held in the Ballroom of the Hotel Statler at 10:20 p.m., immediately following the evening meeting. The program, largely in the nature of variety and vaudeville, will be given by professionals. Light refreshments and beer will be served. Admission will be limited to those who display the official registration badge. Fellows and Associates, local and visiting physicians and the technical exhibitors are invited to attend the Smoker as guests of the College. Men only.

WEDNESDAY, APRIL 3, 1940

CONVOCATION OF THE COLLEGE—8:30 p.m., Music Hall, Public Auditorium. All Masters and Fellows of the College, and those to be received into Fellowship, should be present. Newly elected Fellows who have not yet been received into Fellowship are requested to assemble (room to be announced later) at 7:45 o'clock, preparatory to the formation of the procession. They will occupy especially reserved seats in the central section of the Music Hall, to which they will be conducted by the Convocation Marshal promptly at 8:30 o'clock. It is suggested that all appear in evening dress.

The Convocation is open to all physicians and their families generally. A cordial invitation is also issued to such of the general public as may be interested.

The Convocation program will include an address by the President of the College, the presentation of newly elected Fellows by the Secretary General, conferring of Fellowships, award of the John Phillips Memorial Medal, announcement of the Research Fellowships awarded for 1940 by the College, and the presentation of the Annual Convocation Address by Charles F. Martin, M.D., M.A.C.P., Emeritus Dean and Emeritus Professor of Medicine, McGill University Faculty of Medicine, President of the Canadian Society of Occupational Therapy, and President of the Art Association of Montreal, Montreal, Canada. It is particularly appropriate for Dr. Martin to address the College on the occasion of its Convocation. He is the only remaining Master of the College and he was the President of the College, 1928-29, during the period of reorganization and shaping of new policies and destinies of the organization.

The Presidential Reception, with dancing, will follow in the Ballroom of the Hotel Statler one-half hour after the termination of the exercises. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception at the Hotel Statler.

THURSDAY, APRIL 4, 1940

THE ANNUAL BANQUET OF THE COLLEGE will be held in the Ballroom of the Hotel Statler at eight o'clock, Thursday evening. Dr. Howard T. Karsner, General Chairman of the Twenty-fourth Annual Session of the College, will be the Toastmaster. The address of the evening will be given by Mr. Grove Patterson, Editor of the Toledo Blade. Mr. Patterson is well known as an interesting and entertaining speaker. His address is entitled, "Peeps at the Presidents," referring, of course, to the Presidents of the United States.

\* Buffet luncheon served.

All members of the College, physicians of Cleveland and visitors attending the Session, with their families and friends, are cordially invited. Tickets should be purchased at the Registration Bureau by Wednesday afternoon—price, \$4.00.

### PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The headquarters of the Women's Entertainment Committee will be located in the Pine Room, mezzanine floor, Hotel Statler. Each visitor will receive a program of the activities planned for her entertainment by the Committee. A secretary will be in charge to assist visitors in arranging their program. Visiting women are requested to register *immediately* after arrival. Information concerning theaters, restaurants and places of entertainment will be available at the registration desk.

Members of the Committee will be at the place of registration and will wish to do everything in their power to make the visit to Cleveland pleasant and memorable. Inasmuch as the places available for certain of the events are limited, it is urgently requested that each Fellow or Associate, who will be accompanied by ladies, return the card accompanying the program, as promptly as possible. It is necessary for the Committee to conclude its arrangements in advance of the time of meeting.

Upon registration, the ladies are requested to confirm any reservations they have made and to make such additional reservations as they wish.

#### MONDAY, APRIL 1, 1940

*Morning:* Registration, Hotel Statler.

*Afternoon:* 4:00 to 5:30 o'clock. Complimentary tea at the Women's City Club, Bulkley Building, Euclid Avenue, two blocks east of Hotel Statler.

#### TUESDAY, APRIL 2, 1940

*Afternoon:* 12:30 p.m. Luncheon and Style Show, The Higbee Company, Public Square, nine short blocks from Hotel Statler. \$1.25 per person.

#### WEDNESDAY, APRIL 3, 1940

*Noon:* "Brunch" at Wade Park Manor, followed by Playlet, "Mr. Godey Presents." Tickets; \$1.50. Wade Park Manor is about four miles from Hotel Statler and can be reached by street car or taxicab.

Nearby are the Cleveland Museum of Art and the Garden Center. Registration badges admit to both, and visitors are welcome.

*Evening:* 8:30 p.m. Convocation in Music Hall of Public Auditorium, followed by President's Reception in Ballroom of Hotel Statler.

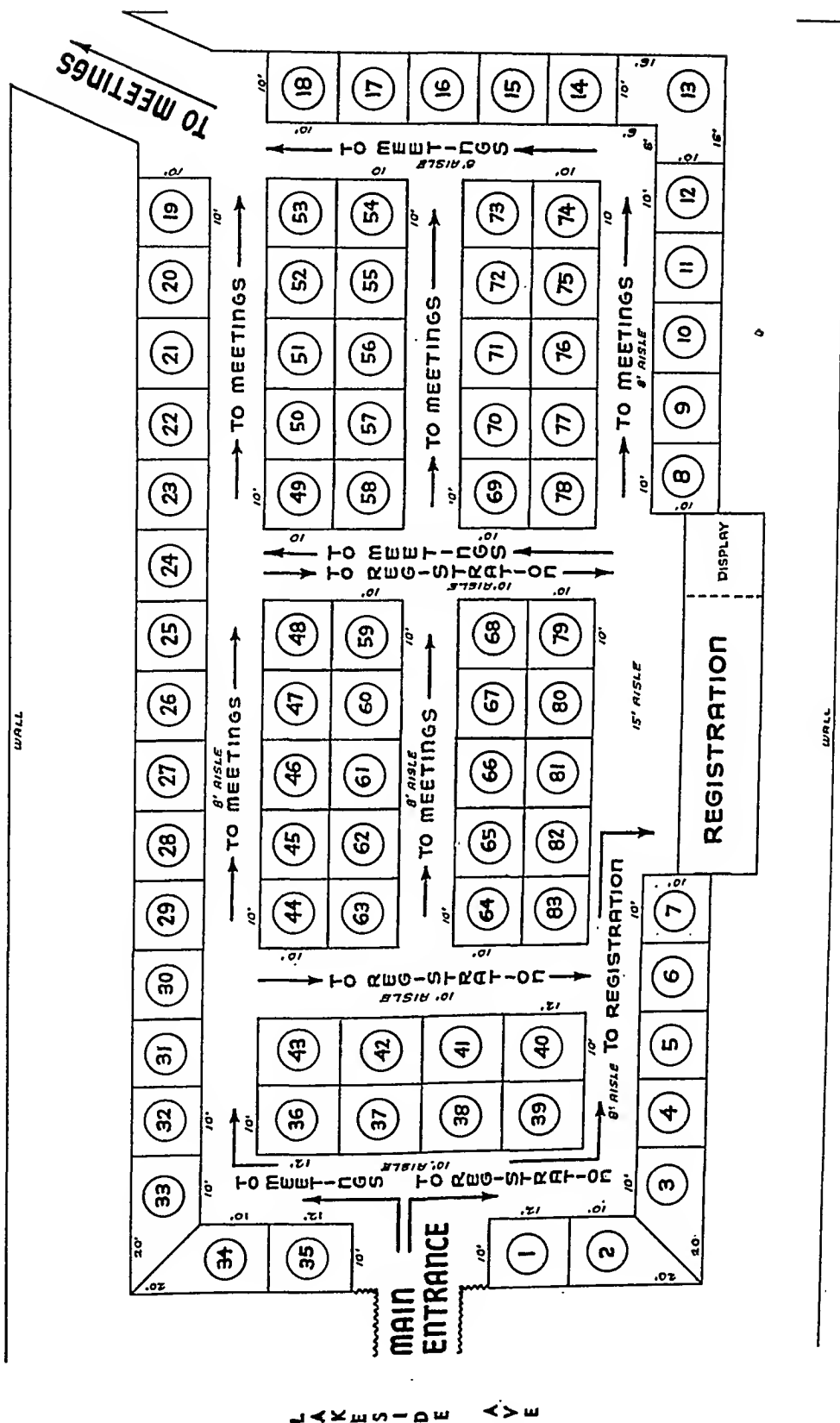
#### THURSDAY, APRIL 4, 1940

*Afternoon:* 3:00 to 5:00 o'clock. Complimentary tea at Cleveland Skating Club, 2106 East 130th Street, and amateur exhibition of figure skating. Transportation by taxicab will be provided. Limited to 200 guests.

*Evening:* 8:00 p.m. Annual Banquet of the College, Ballroom, Hotel Statler.

**FLOOR PLAN OF THE TECHNICAL EXHIBIT**

**EAST 6TH STREET**



## SPECIAL FEATURES

(Concluded)

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the main floor of the Cleveland Public Auditorium.

By official action of the Board of Regents of the College, the technical exhibits have been raised to a higher level of excellence through the elimination of all irrelevant and non-scientific entries. The rules adopted governing this Exhibit are as follows:

- (1) Exhibitors shall be admitted on invitation only;
- (2) The initial approved "Invitation List" shall be made up by the Committee and the Executive Secretary. Both the firm and the product must be approved. Preference shall be given to exhibits of a scientific nature, such as pharmaceuticals, equipment and medical books;
- (3) Additions to the initial approved "Invitation List" may be made by the Committee after application by firms, with the requirement that they submit complete literature concerning their products and their organization;
- (4) The "Invitation List" may be revised annually on the recommendation of the Committee.

The Committee on Exhibits has approved each exhibit before extending invitations. Members and visiting physicians will find these exhibits more interesting and more beneficial than the usual "commercial exhibit." The exhibits have been selected because they are particularly representative of the interests of Internal Medicine and its allied specialties. Here conveniently assembled will be the leading medical books, pharmaceuticals, apparatus and appliances, specialized physicians' furniture and other products, making up much of the important armamentarium of medical practice. Each doctor should take advantage of this opportunity to inspect the latest developments in these lines, not only for the educational and practical value they offer, but also to demonstrate their interest in and courtesy toward these allies of the medical profession and of the College. These exhibitors and their displays merit some special attention on the part of our members because they make a large contribution, educational as well as financial, to the Annual Sessions of the College. Special intermissions in the general program have been arranged, providing additional time for the inspection of exhibits.

## LIST OF EXHIBITORS

(Not yet complete)

	<i>Space</i>
Jones Metabolism Equipment Company, Chicago, Ill.....	1
The G. F. Harvey Company, Saratoga Springs, N. Y.....	2
The Williams & Wilkins Company, Baltimore, Md.....	3
Frober-Faybor Co., Cleveland, Ohio.....	4
Hille Laboratories, Chicago, Ill.....	5
John Wyeth & Bro., Inc., Philadelphia, Pa.....	6
W. B. Saunders Company, Philadelphia, Pa.....	7
Kalak Water Co. of New York, Inc., New York, N. Y.....	8
Davies, Rose & Co., Ltd., Boston, Mass.....	9
Cameron Surgical Specialty Co., Chicago, Ill.....	10
Parker, White & Heyl, Inc., Danbury, Conn.....	11
American Hospital Supply Corporation, Chicago, Ill.....	12



Cambridge Instrument Co., Inc., New York, N. Y.....	13
Ralston Purina Company, Inc., St. Louis, Mo.....	14
Mallinckrodt Chemical Works, St. Louis, Mo.....	15
The Macmillan Company, New York, N. Y.....	18
Paul B. Hoeber, Inc., New York, N. Y.....	19
Devereux Schools, Inc., Berwyn, Pa.....	20
Becton, Dickinson & Co., Rutherford, N. J.....	21-22
The Cream of Wheat Corporation, Minneapolis, Minn.....	23
Merck & Co. Inc., Rahway, N. J.....	24-25
W. F. Prior Company, Inc., Hagerstown, Md.....	26
Ayerst, McKenna & Harrison (U. S.) Limited, Montreal, Que., Canada.....	27
Cameron Surgical Specialty Co., New York, N. Y.....	28
Schering Corporation, Bloomfield, N. J.....	29
The C. V. Mosby Company, St. Louis, Mo.....	30
The Arlington Chemical Company, Yonkers, N. Y.....	31
Medical Case History Bureau, New York, N. Y.....	32
Warren E. Collins, Inc., Boston, Mass.....	33
Burroughs Wellcome & Co. (U. S. A.) Inc., New York, N. Y.....	34
Frederick Stearns & Company, Detroit, Mich.....	35
J. B. Lippincott Company, Philadelphia, Pa.....	36
Lederle Laboratories, Inc., New York, N. Y.....	37-38-39
General Electric X-Ray Corporation, Chicago, Ill.....	40-41
Eli Lilly & Company, Indianapolis, Ind.....	42-43
LaMotte Chemical Products Company, Baltimore, Md.....	44
Smith, Kline & French Laboratories, Philadelphia, Pa.....	45-46
Gerber Products Company, Fremont, Mich.....	47
Oxford University Press, New York, N. Y.....	48
Vegex, Incorporated, New York, N. Y.....	49
E. R. Squibb & Sons, New York, N. Y.....	50-51
The Muller Laboratories, Baltimore, Md.....	52
Sanborn Company, Cambridge, Mass.....	53
Winthrop Chemical Company, Inc., New York, N. Y.....	54-55
The Maltine Company, New York, N. Y.....	56
Riedel-de Haen, Inc., New York, N. Y.....	57
Petrolagar Laboratories, Inc., Chicago, Ill.....	58
Bilhuber-Knoll Corp., Orange, N. J.....	59
Charles B. Knox Gelatine Co., Inc., Johnstown, N. Y.....	60
Lea & Febiger, Philadelphia, Pa.....	63
Ciba Pharmaceutical Products, Inc., Summit, N. J.....	64-65
Kellogg Company, Battle Creek, Mich.....	66
F. A. Davis Company, Philadelphia, Pa.....	67
S. M. A. Corporation, Chicago, Ill.....	68
D. Appleton-Century Co., Inc., New York, N. Y.....	69
H. J. Heinz Company, Pittsburgh, Pa.....	70
Doak Company, Incorporated, Cleveland, Ohio.....	72
Parke, Davis & Company, Detroit, Mich.....	73
Mead Johnson & Company, Evansville, Ind.....	74-75
The Wm. S. Merrell Company, Cincinnati, Ohio.....	76
Thomas Nelson & Sons, New York, N. Y.....	77
Scientific Sugars Co., Columbus, Ind.....	78
Picker X-Ray Corporation, New York, N. Y.....	79
Gradwohl Laboratories, St. Louis, Mo.....	80
The Medical Bureau, Chicago, Ill.....	81
Laboratory Nativelle, New York, N. Y.....	82
The E. L. Patch Company, Boston, Mass.....	83

## OUTLINE OF CLEVELAND SESSION

Municipal Auditorium events are indicated in bold type

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	April 1	April 2	April 3	April 4	April 5
9:00 a.m. to 12:00 m.	Morning free Registration, Exhibits, etc.	Hospital Clinics	Hospital Clinics	Hospital Clinics	Hospital Clinics
		Morning Lectures (10:00- 12:00)	Morning Lectures (10:00- 12:00)	Morning Lectures (10:00- 12:00)	Morning Lectures (10:00- 12:00)
12:00 m. to 1:00 p.m.	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
1:00 p.m. to 2:00 p.m.		Panel Discussions	Panel Discussions	Panel Discussions	Panel Discussions
2:00 p.m. to 5:30 p.m.	1st General Session	3d General Session	4th General Session	5th General Session	6th General Session
5:30 p.m. to 8:00 p.m.	Dinner	Dinner	Dinner	Annual Business Meeting	
8:00 p.m. to 11:00 p.m.	2d General Session followed by SMOKER		CONVOCATION, followed by President's Reception	ANNUAL BANQUET	

## GENERAL SESSIONS

The program of the General Sessions offers as usual a wide variety of subjects, each chosen because of its current interest and importance. In every instance, the speaker has a personal interest in his subject and can be counted upon to present new and important material. The College is fortunate in having a high percentage of the speakers from its own membership and in welcoming new guests to its program.

With the coöperation of the Surgeons General of the Army and Navy, one session has been arranged to present various matters of military interest to all in view of present-day conditions. Included are papers on aviation and submarine medical problems.

Among the newer topics to be presented are the relation of the endocrines to edema formation; the occurrence of vitamin deficiencies in gastrointestinal conditions and the very suggestive new work on the use of agents obtained from soil microorganisms in the treatment of experimental infections. Treatment is well represented by papers on the surgical therapy of hypertension; a report on the newest drug of the sulfapyridine type, also on one of the newer respiratory stimulants. In the final session four papers on psychosomatic medicine are grouped together to form an authoritative symposium.

The mention of these few papers neglects the many other equally important papers in other fields of medicine.

## GENERAL SESSIONS PROGRAM

Cleveland Public Auditorium

## FIRST GENERAL SESSION

Monday Afternoon, April 1, 1940

Presiding Officer

Howard T. Karsner, F.A.C.P., Cleveland, Ohio

p.m.

2:30 Addresses of Welcome:

HOWARD T. KARSNER, F.A.C.P., General Chairman, Twenty-fourth Annual Session; Professor of Pathology and Director of Institute of Pathology, Western Reserve University.

HON. HAROLD H. BURTON, Mayor of the City of Cleveland.

WINFRED G. LEUTNER, President of Western Reserve University.

PARKE G. SMITH, President of the Ohio State Medical Society.

RUSSELL L. HADEN, F.A.C.P., President, The Academy of Medicine of Cleveland.

TORALD SOLLMANN, F.A.C.P., Dean, School of Medicine, Western Reserve University.

Response to Addresses of Welcome:

O. H. PERRY PEPPER, F.A.C.P., President, American College of Physicians; Professor of Medicine, University of Pennsylvania.

3:45 INTERMISSION.

4:00 Specialization in General Medicine.

WILLIAM B. BREED, F.A.C.P., Associate in Medicine, Harvard University Medical School; Physician, Massachusetts General Hospital; Boston, Mass.

## 4:20 Postgraduate Education.

HUGH J. MORGAN, F.A.C.P., Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

## 4:40 The First Four Years of the American Board of Internal Medicine and Its Apparent Influence on Medical Education and Practice.

ERNEST E. IRONS, F.A.C.P., Clinical Professor of Medicine and Chairman of Department, Rush Medical College; Chairman, American Board of Internal Medicine; Chicago, Ill.

## 5:00 ADJOURNMENT.

## SECOND GENERAL SESSION

Monday Evening, April 1, 1940

Presiding Officer

James D. Bruce, F.A.C.P., Ann Arbor, Mich.

## SYMPOSIUM ON MILITARY MEDICINE

p.m.

## 8:00 Medical Problems Encountered in Military Service.

COL. CHARLES C. HILLMAN, M.C., U.S.A. (F.A.C.P.).

## 8:20 Epidemiology in the Army.

LT. COL. JAMES S. SIMMONS, M.C., U.S.A. (F.A.C.P.).

## 8:40 Organization and Administration of the Medical Department.

LT. COL. CHARLES B. SPRUIT, M.C., U.S.A. (By invitation.)

## 9:00 Developments in Aviation Medicine.

CAPT. HARRY G. ARMSTRONG, M.C., U.S.A. (Associate, A.C.P.).

## 9:20 Tetanus Toxoid Immunization in the U. S. Navy.

COMDR. W. W. HALL, M.C., U.S.N. (F.A.C.P.).

## 9:40 Physiological Effects of Increased Barometric Pressure; Application of Findings to Clinical Medicine.

LT. ALBERT R. BEHNKE, M.C., U.S.N. (By invitation.)

## 10:00 ADJOURNMENT.

10:20 o'Clock

## SMOKER

Ballroom, Hotel Statler

A diverting and amusing program has been arranged. Admission by registration badge. Men only.

## THIRD GENERAL SESSION

Tuesday Afternoon, April 2, 1940

Presiding Officer

J. Morrison Hutcheson, F.A.C.P., Richmond, Va.

p.m.

## 2:00 Results of Treatment of Essential Hypertension: Medical versus Surgical.

E. V. ALLEN, F.A.C.P., Associate Professor of Medicine, University of Minnesota (Mayo Foundation); Chief of Section in Division of Medicine, Mayo Clinic; Rochester, Minn., and

- A. W. ADSON (by invitation), Professor of Neurosurgery, University of Minnesota (Mayo Foundation); Chief of Department of Neurosurgery, Mayo Clinic; Rochester, Minn.
- 2:30 Prevention of Pernicious Anemia—Recognition of the Latent Stage in Relatives.  
JOHN M. ASKEY, F.A.C.P., Assistant Professor of Clinical Medicine, University of Southern California School of Medicine, Los Angeles, Calif.
- 2:45 Endocrine Abnormalities in Puberty.  
JOSEPH C. AUB (by invitation), Associate Professor of Medicine, Harvard University Medical School, Boston, Mass., and  
IRA NATHANSON (by invitation), Boston, Mass.
- 3:15 A Study of the Acute Leukoses.  
JOSEPH KAUFMANN, F.A.C.P., Assistant Professor of Medicine, McGill University Faculty of Medicine, Montreal, Que., Canada, and  
LOUIS LOWENSTEIN (by invitation), Montreal, Que., Canada.
- 3:35 INTERMISSION.
- 4:00 Pancreatitis: An Analysis of Types and Causes.  
KENNETH M. LYNCH, F.A.C.P., Professor of Pathology and Vice Dean, Medical College of the State of South Carolina, Charleston, S. C.
- 4:15 Changes in the Human Heart During Growth and Hypertrophy.  
JOSEPH T. WEARN, F.A.C.P., Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.
- 4:35 Pathogenesis of Banti's Disease.  
WILLIAM P. THOMPSON (Associate, A.C.P.), Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.
- 5:00 ADJOURNMENT.

## FOURTH GENERAL SESSION

Wednesday Afternoon, April 3, 1940

Presiding Officer

Allen A. Jones, F.A.C.P., Buffalo, N. Y.

p.m.

- 2:00 Hematological Aspects of Space Consuming Lesions of the Bone Marrow.  
STACY R. METTIER, F.A.C.P., Associate Professor of Medicine, University of California Medical School, San Francisco, Calif.
- 2:15 The Comparative Effectiveness of Sulfathiazol and Sulfapyridine in Pneumococcal Pneumonia.  
H. F. FLIPPIN (Associate, A.C.P.), Instructor in Medicine, University of Pennsylvania School of Medicine and Graduate School of Medicine, Philadelphia, Pa., and  
LEON SCHWARTZ (by invitation), Assistant Instructor in Medicine, University of Pennsylvania, Philadelphia, Pa.
- 2:30 The Treatment of Ulcerative Colitis with Sulfanilamide.  
E. N. COLLINS, F.A.C.P., Head, Section on Gastrointestinal Diseases, Cleveland Clinic, Cleveland, Ohio.

- 2:50 Concerning the Correlation of the Pathology and Symptoms of Coronary Artery Disease.  
FRED M. SMITH, F.A.C.P., Professor and Head of Department of Theory and Practice of Medicine, State University of Iowa College of Medicine; Editor-in-Chief, American Heart Journal; Iowa City, Iowa.
- 3:10 Malarial Coma.  
CONLEY H. SANFORD, F.A.C.P., Professor of Medicine and Chief of Division of Medicine, University of Tennessee College of Medicine, Memphis, Tenn.;  
P. T. CRAWFORD (Associate, A.C.P.), Memphis, Tenn., and  
OTIS S. WARR, JR. (by invitation), Memphis, Tenn.
- 3:30 INTERMISSION.
- 4:00 Rôle of Pituitary in Edema of Nephritis.  
FRANK H. ROBINSON\* (Associate, A.C.P.), Jamestown, N. Y., and  
LEE E. FARR (by invitation), Associate in Medicine, The Rockefeller Institute for Medical Research, New York, N. Y.
- 4:20 The Rôle of the Gonadal and Adrenal Cortical Hormones in the Production of Edema.  
GEORGE W. THORN, F.A.C.P., Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.
- 4:40 The Relation of Listerella to Human Infection.  
LOUIS A. JULIANELLE (by invitation), Associate Professor of Applied Bacteriology and Immunology, Washington University School of Medicine, St. Louis, Mo.
- 5:00 ADJOURNMENT.

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### ANNUAL CONVOCATION

Wednesday Evening, April 3, 1940

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8:30 o'Clock

Music Hall, Public Auditorium

All members of the profession and the general public are cordially invited. No special admission tickets will be required.

1. The President's Address.

O. H. Perry Pepper.

2. Presentation of Newly-Elected Fellows and Recital of the Pledge.

George Morris Piersol, Secretary-General.

3. Presentation of John Phillips Memorial Medal for 1939-40.

4. Announcement of Research Fellows of the College for 1940.

5. Convocational Address:

CHARLES F. MARTIN, M.A.C.P., Emeritus Dean and Emeritus Professor of Medicine, McGill University Faculty of Medicine; President, Alexandra Hospital; President, Canadian Society of Occupational Therapy; President, Art Association of Montreal, Montreal, Que., Canada.

\* Deceased since program assignment.

*President's Reception*

The Reception and Dance will follow one-half hour after the completion of this program, and will be held in the Ballroom of the Hotel Statler. Newly-inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception at the Hotel Statler.

## FIFTH GENERAL SESSION

Thursday Afternoon, April 4, 1940

Presiding Officer

Charles H. Cooke, F.A.C.P., Asheville, N. C.

p.m.

- 2:00 Industrial Medicine as a Specialty and Its Relation to General Practice.  
GEORGE H. GEHRMANN, F.A.C.P., Medical Director, E. I. duPont de Nemours and Company, Wilmington, Del.
- 2:20 The Effect of Specific Agents Extracted from Soil Microorganisms upon Experimental Bacterial Infections.  
RENÉ J. DUBOS (by invitation), Associate Member, Rockefeller Institute for Medical Research, New York, N. Y.
- 2:50 Vitamin Deficiencies and Gastrointestinal Disease.  
THOMAS T. MACKIE, F.A.C.P., Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.
- 3:10 Vitamins and Peptic Ulcer.  
HENRY FIELD, JR. (by invitation), Associate Professor of Internal Medicine, University of Michigan, Ann Arbor, Mich.;  
WILLIAM D. ROBINSON (by invitation), Ann Arbor, Mich.; and  
DANIEL MELNICK (by invitation), Ann Arbor, Mich.
- 3:30 INTERMISSION.
- 4:00 The Importance of Allowing Time for "Physiological Adjustment" in Establishing the Diet in Diabetes.  
R. R. SNOWDEN, F.A.C.P., Associate Professor of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pa.
- 4:15 The Clinical Significance of Iron in the Blood.  
REGINALD FITZ, F.A.C.P., Wade Professor of Medicine, Boston University School of Medicine, Boston, Mass.
- 4:30 Observations upon the Effect of Coramine in Certain Cardiac States.  
WILLIAM D. STROUD, F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., and  
PAUL H. TWADDLE (by invitation), Morris W. Stroud, Jr. Fellow in Cardiology, Pennsylvania Hospital, Philadelphia, Pa.
- 4:45 ADJOURNMENT, to be followed by

## ANNUAL BUSINESS MEETING

*The Annual Business Meeting* of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Official reports will be made by the Treasurer and the Executive Secretary; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. James D. Bruce, Ann Arbor, Mich., will be inducted into office.

## THE ANNUAL BANQUET OF THE COLLEGE

Thursday Evening, 8:00 o'Clock

Ballroom, Hotel Statler

(Procure Tickets at the Registration Bureau)

Consult Special Banquet Program

Toastmaster: Howard T. Karsner, F.A.C.P., Cleveland, Ohio.

Address: "Peeps at the Presidents."

Mr. Grove Patterson, Editor, Toledo Blade, Toledo, Ohio.

## SIXTH GENERAL SESSION

Friday Afternoon, April 5, 1940

Presiding Officer

Gerald B. Webb, F.A.C.P., Colorado Springs, Colo.

p.m.

2:00 Social Components in Medicine.

EDWARD L. BORTZ, F.A.C.P., Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.

2:20 Illness in Families as Influenced by a Combined Medical, Psychiatric and Social Approach.

HENRY B. RICHARDSON, F.A.C.P., Associate Professor of Clinical Medicine, Cornell University Medical College, New York, N. Y.

2:40 Emotion and Bodily Changes—A Survey of Recent Psychosomatic Studies.

H. FLANDERS DUNBAR (by invitation), Associate in Psychiatry, Columbia University; Editor, Psychosomatic Medicine, New York, N. Y.

3:00 The Treatment of Illness of Emotional Origin by the Internist.

EDWARD WEISS, F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine, Philadelphia, Pa.

3:20 Post Hyperthyroid Conditions.

HENRY M. THOMAS, JR., F.A.C.P., Associate in Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

3:40 Blood Cholinesterase in Rheumatic Fever.

MARK P. SCHULTZ, F.A.C.P., Surgeon, U. S. Public Health Service, Washington, D. C.

4:05 Observations Relative to Prolonged Partial Occlusion of the Small Intestine.

LAY MARTIN, F.A.C.P., Associate in Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

4:25 Tularemic Pneumonia.

G. GILL RICHARDS, F.A.C.P., Visiting Physician, Dr. W. H. Groves, Latter-Day Saints Hospital; Member, American Board of Internal Medicine; Salt Lake City, Utah.

4:40 Bronchostenosis Complicating Allergic and Infectious Asthma.

LOUIS E. PRICKMAN, F.A.C.P., Assistant Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant, Mayo Clinic, Rochester, Minn.; and

HERMAN J. MOERSCH, F.A.C.P., Associate Professor of Medicine, University of Minnesota (Mayo Foundation), Rochester, Minn.

5:00 ADJOURNMENT.



## MORNING LECTURES

The Lectures have been of increasing popularity and are being scheduled this year between 10:00 a.m. and 12:00 m., daily, from Tuesday to Friday, inclusive. An hour is assigned to each, which permits the lecturer to complete a rounded discussion of his subject. It is true they conflict with the Clinics, but they offer a very different type of presentation and undoubtedly the Lectures will appeal to many of the members.

Each of the lecturers is an authority on the subject he will present. The topics are varied; each is important and lends itself to presentation as a well-balanced review. The colored motion pictures of the Growth of the Chick Embryo is a different type of presentation of fascinating interest.

The Lectures will be open to all members and guests of the College.

*Admission by regular registration badge.*

Tuesday Morning, April 2, 1940

Public Auditorium

Presiding Officer

Maurice C. Pincoffs, F.A.C.P., Baltimore, Md.

a.m.

10:00 The Diagnosis of Leukemia.

LOUIS HAMMAN, F.A.C.P., Associate Professor of Clinical Medicine,  
Johns Hopkins University School of Medicine, Baltimore, Md.

11:00 The Differential Diagnosis of Coronary Insufficiency.

WILLIAM J. KERR, F.A.C.P., Professor of Medicine and Chairman of  
Department of Medicine, University of California Medical School;  
Member, American Board of Internal Medicine; San Francisco,  
Calif.

Wednesday Morning, April 3, 1940

Public Auditorium

Presiding Officer

George Morris Piersol, F.A.C.P., Philadelphia, Pa.

a.m.

10:00 Thyroid Disease.

JAMES HOWARD MEANS, F.A.C.P., Jackson Professor of Clinical Medicine,  
Harvard University Medical School; Chief of Medical Services,  
Massachusetts General Hospital, Boston, Mass.

11:00 Problems of Acute Infections.

JOHN H. MUSSER, F.A.C.P., Professor of Medicine, Tulane University  
of Louisiana School of Medicine, New Orleans, La.

Thursday Morning, April 4, 1940

Public Auditorium

Presiding Officer

Edward L. Bortz, F.A.C.P., Philadelphia, Pa.

a.m.

10:00 Clinical Manifestations of Nicotinic Acid and Riboflavin Deficiency (Pellagra).

V. P. SYDENSTRICKER, F.A.C.P., Professor of Medicine, University of Georgia School of Medicine; Physician-in-Chief, University Hospital, Augusta, Ga.

11:00 The Growth and Development of Chick Embryos (Motion Picture).

BRADLEY M. PATTEN (by invitation), Professor of Anatomy, University of Michigan, Ann Arbor, Mich.

Friday Morning, April 5, 1940

Public Auditorium

Presiding Officer

James E. Paullin, F.A.C.P., Atlanta, Ga.

a.m.

10:00 Polycythemia.

RUSSELL L. HADEN, F.A.C.P., Chief of Medical Division, Cleveland Clinic, Cleveland, Ohio.

11:00 Hypotension.

A. B. BROWER, F.A.C.P., Cardiologist and Member of Senior Medical Service, Miami Valley Hospital; Member of Senior Medical Staff, St. Elizabeth Hospital, Dayton, Ohio.

### PANEL DISCUSSIONS

The President of the College and the Cleveland Committee on Arrangements have replaced the Round Tables with Panel Discussions at this Session. Instead of having one leader, several distinguished authorities in each of the fields will conduct the discussions. They have been requested to open the discussions promptly and to terminate them sharply at the expiration of the hour.

The Panel Discussions will be held from 1:00 p.m. to 2:00 p.m. on Tuesday, Wednesday, Thursday and Friday in the Cleveland Public Auditorium.

The leaders are prepared to discuss any phase of the subject which has been assigned to them. When application is made for tickets, it is suggested that the applicant submit in writing any question or phase of the subject which he especially wishes discussed. Questions may also be submitted at least twenty-four hours before the discussion to the General Chairman. A certain number of these request questions may not be answered on account of lack of time. Leaders will answer those questions which seem to be most in demand.

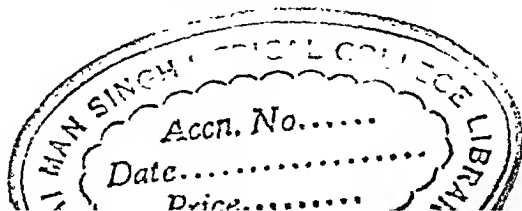
*Members should make application for Panel tickets on the regular application form accompanying the formal program, or at the Registration Bureau at the Public Auditorium.*

### PROGRAM OF SPECIAL CLINICS AND DEMONSTRATIONS

The staffs of seven hospitals will participate and there will be in many instances especially invited distinguished visitors to give clinics. There are eleven auditoriums available with a total capacity of 2,312. They vary in seating capacity from 60 to 400 and it will therefore be advisable to make reservations, at least for the smaller places, as soon as the formal program is received.

In addition to the clinics, there will be talks on research problems of clinical interest and on recent advances in some of the fields. This is especially true of the one morning session at the Babies and Childrens Hospital.

Details of the clinics and demonstrations will be given in full in the formal program.



PANEL DISCUSSIONS  
Public Auditorium

Room	Hall "A" South Wing	Hall "B" South Wing	Clubroom "B" North Wing	Clubroom "A" North Wing
CAPACITY	325	325	500	225
Tuesday April 2 1:00 to 2:00 p.m.	I EDEMA AND NEPHRITIS Joseph M. Hayman, Jr. Louis Leiter Robert F. Loeb John P. Peters	II DRUG THERAPY IN HEART DISEASE M. H. Nathanson Fred M. Smith William D. Stroud	III VITAMIN B IN INTERNAL MEDICINE Thomas T. Mackie Julian M. Ruffin Tom D. Spies	IV LYMPHOMATOID DISEASES Raphael Isaacs Henry Jackson, Jr. Franklin R. Miller
Wednesday April 3 1:00 to 2:00 p.m.	V NEWER DRUGS IN THERAPY M. A. Blankenhorn R. F. Parker Torald Sollmann	VI PROBLEMS IN ELECTROCARDIOGRAPHY Arlie R. Barnes Arthur M. Master Harold E. B. Pardee Frank N. Wilson Charles C. Wolferth	VII ALLERGY IN INTERNAL MEDICINE Robert A. Cooke Richard A. Kern Simon S. Leopold Francis M. Rackemann	VIII INDUSTRIAL DISEASES Daniel M. Brumfiel Leroy U. Gardner Carey P. McCord
Thursday April 4 1:00 to 2:00 p.m.	IX GASTRO-ENTEROLOGY Sara M. Jordan T. Grier Miller	X HEMORRHAGIC DISEASES Charles A. Doan Harry P. Smith F. H. Taylor	XI DIABETES H. Rawle Geyelin Howard F. Root	XII ENDOCRINOLOGY OF PUBERTY AND CLIMACTERIUM Joseph C. Aub J. S. L. Brown E. Perry McCullagh
Friday April 5 1:00 to 2:00 p.m.	XIII PROBLEMS IN TUBERCULOSIS Samuel Freedlander R. C. McKay James Alex. Miller Gerald B. Webb	XIV PHYSIOLOGICAL ASPECTS OF CARDIAC DISEASE Soma Weiss Carl J. Wiggers	XV SHOCK TREATMENT OF PSYCHOSES Solomon Katzenelbogen William C. Menninger S. Bernard Wortis	XVI ANEMIA John M. Askey Stacy R. Mettler Cyrus C. Sturgis

Special taxicab rates have been arranged between hotels and hospitals.

It will be necessary to limit admission by ticket only, otherwise there is danger that those who might wish to attend will be disappointed. Overcrowding will not be permitted. Registration blanks for the clinics and demonstrations will be distributed to all members with the formal program. These registration blanks should be filled out and returned to the Executive Secretary of the College at Philadelphia. He will select the appropriate tickets and hold them for members at the Registration Bureau in Cleveland. Reservations by mail cannot be made after March 22, but they may be made in person at the Registration Bureau not later than the evening preceding the clinic desired. Guests are urged to register for the clinics immediately after arrival in Cleveland.

## CLEVELAND

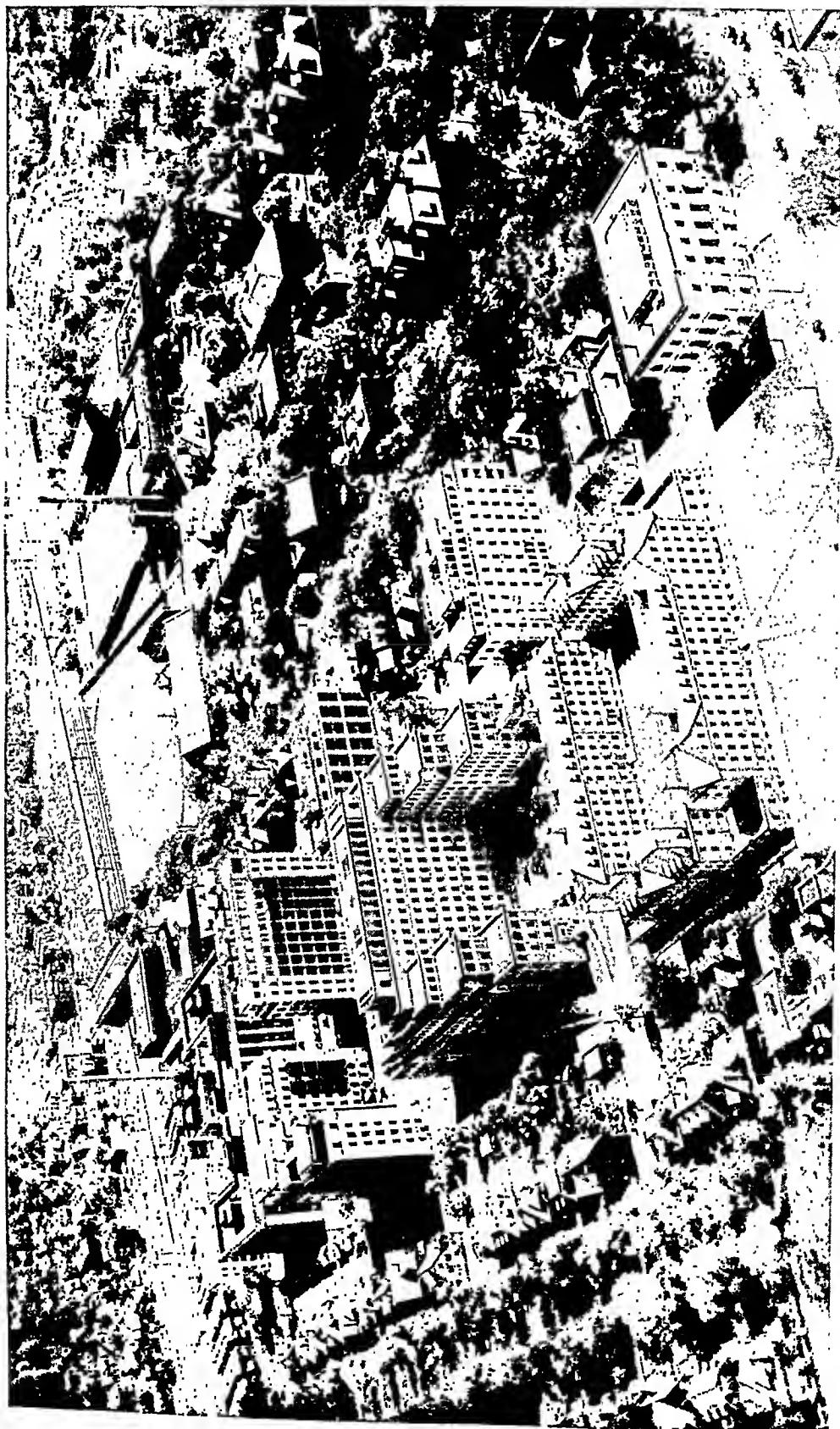
### WHERE WE MEET

CLEVELAND, originally a trading post at the mouth of the Cuyahoga River, has developed as the industrial center of the historic "Western Reserve." This tract of land was part of the original Connecticut charter granted in 1662 by Charles II for the whole area between the forty-first and forty-second parallels extending westward to the Pacific Ocean. In 1786 Connecticut released to the United States title to all except one area which she reserved for herself and called the Connecticut Western Reserve. This extended for 120 miles west from the Pennsylvania border, or approximately to the present city of Sandusky and just south of Akron and Youngstown.

Cleveland was developed as a planned real estate venture at the time of the great western trek into the Ohio country after the Revolution. The Public Square was laid out in 1796 by Moses Cleveland, Yale graduate and attorney. A group of hardy New England Yankees formed the Connecticut Land Company and raised a sum of \$1,200,000. They were a group of substantial citizens whose names have been handed down to succeeding generations and whose descendants are still among the first families of Cleveland. Among them was Samuel Mather, Jr. who was the direct forebear of the Samuel Mather who built the present \$2,500,000 medical school.

Cleveland grew rapidly because it was the natural meeting place for iron ore, coal and limestone. The Great Lakes iron ore deposits are the largest and richest in the world, some (hematite) containing 70 per cent of iron. Iron and steel have been Cleveland's leading industries since 1828 when the first smelter was established. At present her capacity is over 3,000,000 tons of pig iron annually. The first cargo of iron ore from Lake Superior entered Cleveland's harbor in 1852. In 1939 The Lake Carriers Association registered 303 ore boats, two-thirds of them over 10,000 tons. Ore by boat and coal by train meet at Cleveland blast furnaces. Huge unloaders take the ore from the ships almost a carload at a time, over 10,000 tons an hour. Today a greater annual tonnage comes from the Great Lakes to Cleveland than that of Liverpool and more than all of the French ports combined. There are fourteen miles of lakefront protected by a breakwater about six miles long; and extensive docks along the Cuyahoga River banks. The steel industry's leading technical society, The American Society for Metals, with 10,000 members, has its headquarters in Cleveland and will hold its annual "Metal Congress" in Cleveland in 1940 with an anticipated attendance of 30,000.

Cleveland industry has become most diversified, having at present 3,000 industrial plants with an aggregate annual payroll in excess of \$200,000,000 and products with an annual value of \$1,000,000,000. Cleveland leads in



WESTERN RESERVE UNIVERSITY MEDICAL GROUP.

*From front to rear, Nurses' Home, Lakeside Hospital (with Hanna House and Institute of Pathology to right), Maternity, and Babies and Childrens Hospitals and Medical School.*  
*In right foreground, Allen Memorial Medical Library which includes headquarters of the Academy of Medicine.*

the production of all manner of iron and steel products, hardware, paint, malleable castings, electrical machinery and lamps, sewing machines, tractors and auto parts, multigraphs, telescopes, and readymade clothing. The National Electric Lamp Division of the General Electric Company has a 75-acre plant located in East Cleveland and has an elaborate research laboratory in all forms of illumination, some of real significance to medicine. There is hardly a city on the earth where Cleveland-made goods will not be found or a country whose goods are not imported to Cleveland. At least two-thirds of the nation's industries are represented in the city.

Cleveland also is the headquarters of the Fourth Federal Reserve District and as such is the financial center of this American Ruhr, the midwest manufacturing district including Pittsburgh, Youngstown, Toledo and Detroit, as busy and rich a territory as there is on the face of the earth. This Federal Reserve District is exceeded only by New York and Chicago in the United States in the volume of business.

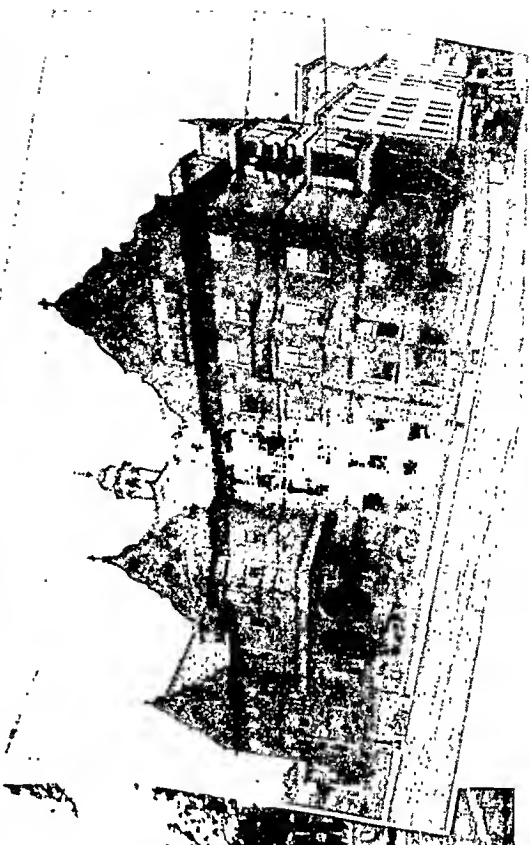
Cleveland is a natural transportation center. It is easy to reach by rail, water, air or motor. Trunk railroad lines, motor coach and airlines enter the city from all major travel centers. The New Union Passenger Terminal on the Public Square is one of the world's finest. This great building and its companion group have been called a "City Within a City." It is continuous with the Cleveland Hotel and five minutes walk from the Convention Hall. From this, Cleveland's famous Mall extends to the lake front, a \$40,000,000 development covering 17 acres for a group of public buildings.

Cleveland's 1,040 acre airport is the largest municipally owned aviation field in the country and the usual site of the National Air Races. The Eastern Division headquarters of the transcontinental day and night mail route is located on the main field. Passenger and express service is available to every point in the country. The second field is occupied by the Ohio National Guard flying unit. The average ship movement is 3,500 per month. The port has twelve hangars. Service is available for all types of ships and motors. A visit to the Airport at night is most interesting. Planes may be seen landing and taking off by the light of a 500,000,000 candle power flood light.

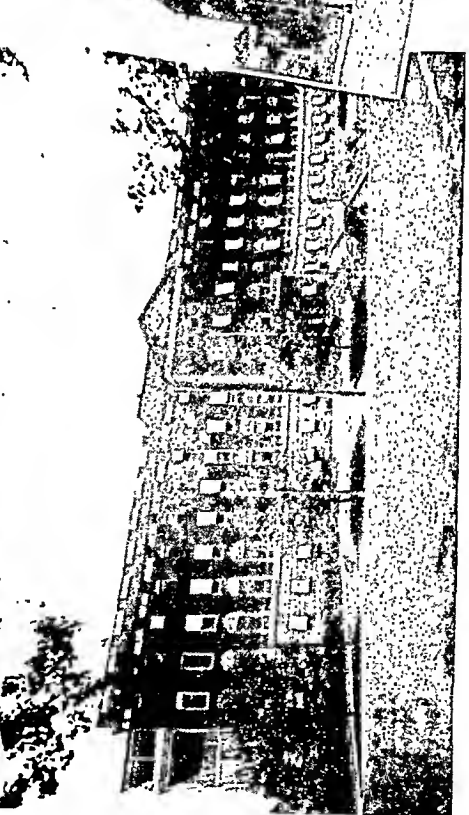
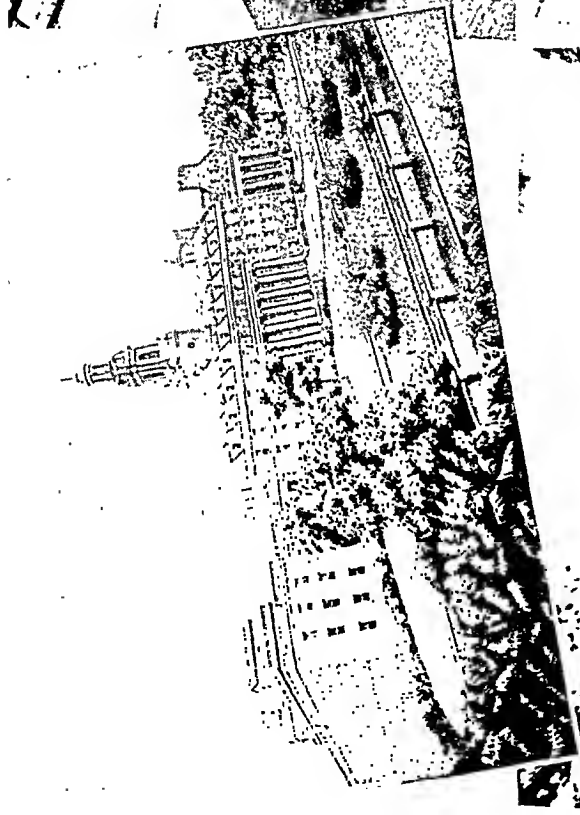
The Metropolitan Park System of Greater Cleveland combines into one continuous outer encircling parkway the more important valleys and glens in Cuyahoga County and parts of the neighboring counties. Nine park reservations are included in the project which consists of approximately 90 miles of parkway and 15,000 acres of grounds. Two golf courses in Rocky River Valley are included in the system.

#### EDUCATION

Western Reserve University was established in 1826 at Hudson twenty miles to the south; and in 1882 moved to Cleveland leaving the academy at Hudson. Department after department was added until now Western



Upper Left: St. Luke's Hospital.  
Lower Left: Mt. Sinai Hospital.



Upper Right: Charity Hospital.  
Lower Right: St. Alexis Hospital.



Reserve University has 16 colleges and 15,000 students including downtown Cleveland College. The Medical School referred to above is one of the newest and best college medical buildings in the world and is placed in the center of a complete hospital group representing an investment of \$13,000,000. Western Reserve has the only medical school in Northern Ohio, having absorbed two or more older medical schools during its growth. The famous University Circle at East 107th Street and Euclid Avenue,  $3\frac{1}{2}$  miles



Cleveland City Hospital Group.

east of the Public Square, includes in addition to the above the Art Museum, Severance Hall, the Medical Library, the Historical Museum and the Case School of Applied Science. In addition to Western Reserve University and Case School, Cleveland has John Carroll University, Fenn College, 300 public and parochial schools and a group of special institutes for vocational training. The Art Museum is an architectural gem in a colorful setting viewed from Euclid Avenue across the lagoon. Over 300,000 people visit the Museum annually. The city's cultural maturity is attested further by the community interest in the drama. The Play House at East 86th Street provides an outlet for local talent.

The Cleveland Orchestra has done much to carry the story of Cleveland's educational and cultural progress to the rest of the world. This famous musical organization has given concerts in more than half the states in the Union and in Cuba and Canada. Severance Hall at University Circle is the new \$2,500,000 home of the Orchestra.

Unique among medical facilities in American cities is the Allen Memorial Medical Library building at the corner of Adelbert Road and Euclid Avenue. This monumental structure was made possible by a gift from Mrs. Francis

Fleury Prentiss in honor of one of the founders of the library, Dr. Dudley P. Allen, and is the official home of the practicing physicians of Cleveland. Besides the magnificent library, reading rooms and club rooms, the building houses the offices and headquarters of the Academy of Medicine (the county medical society) with auditorium facilities for groups of varying sizes. The Library, with 56,000 volumes, is one of the outstanding institutions of its kind in the country. The Academy of Medicine is a pioneer in the development of health education and community health planning in Cleveland. Its membership of nearly 1700 carries on the work in scientific sections, in numerous committees, by appointees on various welfare boards throughout the city, and by the publication of a monthly bulletin which reaches interested individuals and groups in addition to the membership. The executive office, under the direction of a full-time executive secretary, correlates all activities, and in addition furnishes a twenty-four hour call and information service for the public and the patients of Academy members.

The Cleveland Public Library, a \$5,000,000 building on the Mall, is an outstanding educational feature of this city. Nine and one-half million books are borrowed from the library annually, one million educational volumes are circulated each year through its county library department. Eight million visitors enter the library each year for reading and reference.

Commensurate with the industrial, artistic and educational development, Cleveland has advanced in public health and welfare service attaining first rank in the 1939 competition for the safest and healthiest large city in the country, granted by the Chamber of Commerce of the United States in co-operation with the American Public Health Association. Cleveland's health and welfare activities are grouped under a director, at present Mr. Fred Ramsey, who is a member of the Mayor's cabinet. Health activities are delegated to the Division of Health which is under the direction of a Commissioner of Health, Dr. Harold J. Knapp. The Health Department for many years has maintained the closest coöperative relations with the organized medical profession, the Commissioner of Health meeting regularly with the Council of the Academy of Medicine and its public health and health education committees.

In Cuyahoga County there are 5,532 hospital beds exclusive of sanatoria. Greater Cleveland has a population of 1,280,000 giving an approximate ratio of hospital beds to population of 5 per 1,000. All cases of tuberculosis from Cleveland and Cuyahoga County are hospitalized by the Bureau of Tuberculosis of the Division of Health; they number at present 1,009 cases. Two hundred beds are maintained at the Contagious Division of City Hospital for quarantinable diseases.

Warrensville Farm for charitable and corrective purposes is a striking example of the spirit of Cleveland citizens. This great experiment, which has brought many students of social welfare to Cleveland, occupies 2,000 acres of high ground some seven miles from the city. Here tuberculous patients are cared for in the beautiful and well equipped Sunny Acres Sani-

torium; aged couples are enabled to spend their last years together in a cottage expressly for that purpose; and inmates of the House of Correction are taught useful occupations—in the shops in winter and in the farm fields in summer.

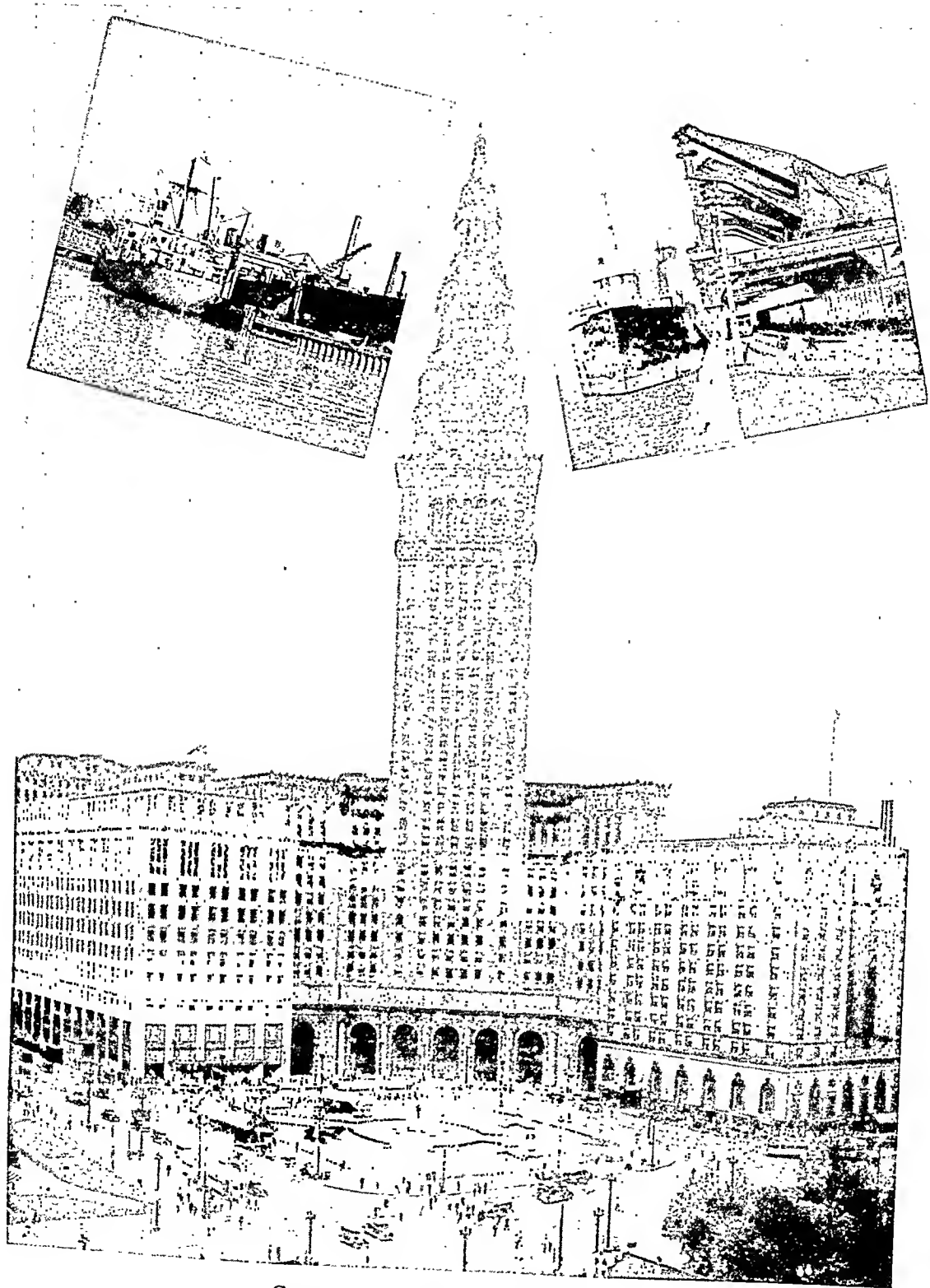
Unofficial health promotion agencies in Cleveland are grouped in the Cleveland Health Council as an agency under the Community Fund. This Council was organized in 1925 by the Professor of Hygiene and Preventive Medicine of Western Reserve Medical School. The Council is now composed of forty-four members. It serves to coördinate all health promotion agencies in the community including the Academy of Medicine, the Cleveland Dental Society, and eleven agencies supported by the Community Fund. The secretary of the Health Council, Mr. Howard W. Green, is an expert in census statistics and demography and carries out researches in relation to the incidence of disease and its correlation with economic factors by census tracts in the community. The findings have medical value and have led to various health education programs for parents such as those in connection with immunizations of school children.

Likewise, Cleveland has pioneered in socio-economic measures in the medical field, especially in group hospitalization and a dispensary admissions plan widely adopted and copied in the United States. The Academy of Medicine is sincerely trying to develop sound measures to adjust the form and cost of medical service to changing social needs. This policy from within the profession is regarded as the best prevention against meddlesome interference from without, especially by politically minded governmental agencies.

The Community Fund, used today by every city of consequence in the United States, originated in Cleveland. Through this centralization of social welfare financing, the amount of money realized for these important activities has been greatly increased. Citizens pledged \$3,250,000 for Cleveland's 1940 welfare and relief needs. There were 490,000 donors. Before the Fund was established, 5,000 givers bore the annual burden. The Community Fund assists 100 local agencies in their welfare and relief work.

### HOSPITALS

The medical center is at Euclid Avenue and East 110th Street. The University Hospitals of Cleveland is a non-profit corporation organized in 1925 which provides a consolidated management for four established hospitals—Lakeside Hospital, Maternity Hospital, Babies and Childrens Hospital, and Rainbow Hospital for Crippled and Convalescent Children. With the exception of Rainbow Hospital, which is located in South Euclid Village, the group is situated on the campus of Western Reserve University, with which the hospitals maintain a teaching affiliation. Here also are located the School of Medicine, the Allen Memorial Medical Library, the School of Dentistry and the Institute of Pathology where Dr. Harry Goldblatt did



GLIMPSES OF INDUSTRIAL CLEVELAND.

Upper Left: Norwegian Freighter Ties Cleveland to World Trade.  
Upper Right: Lake Carrier and Loading Cranes.  
Bottom: Terminal Tower Group from Public Square.

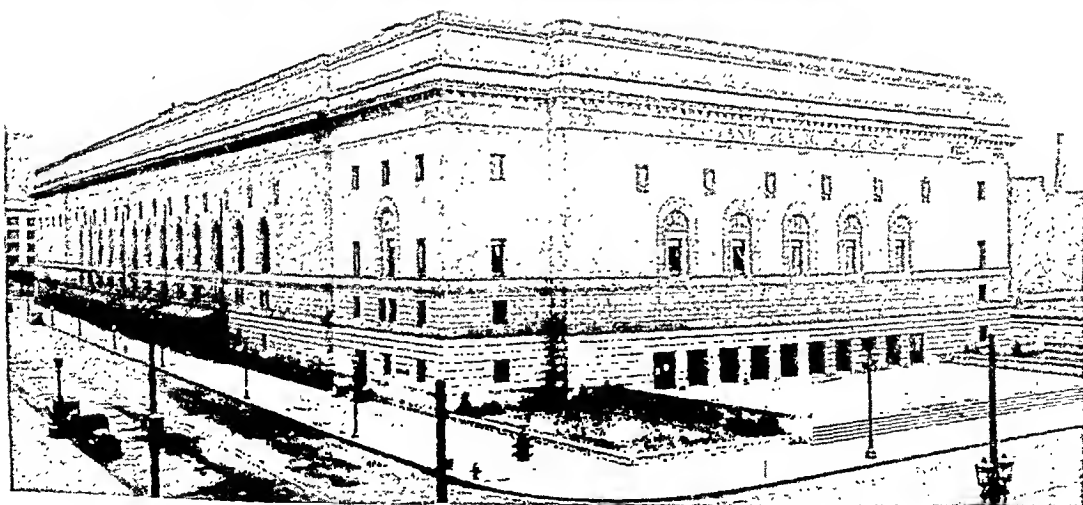
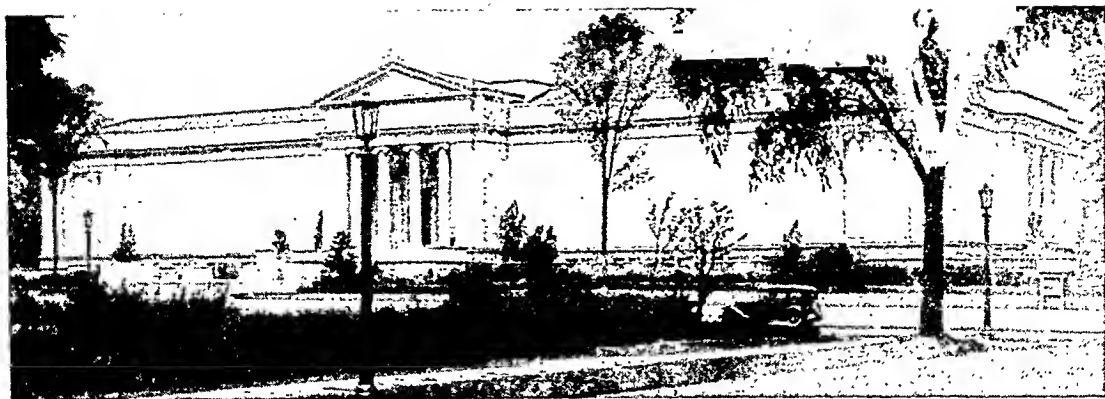
and is doing his work on hypertension and won the John Phillips prize of the College for 1938.

At Maternity Hospital, facilities are provided for the care of 75 private and 51 community service patients in the obstetrical division, and 34 patients on the gynecological service. Babies Dispensary and Hospital represent the pediatric department of the Medical School and have 75 beds. For the special benefits of its little patients, Rainbow Hospital, on Green Road, South Euclid, is built on the cottage, or one floor plan. Convalescent care is given to children crippled by infantile paralysis, bone tuberculosis, rheumatic heart disease and various nutritional deficiencies.



Cleveland Clinic Hospital.

The City Hospital, 3395 Scranton Road, sixth largest general hospital in the United States, is a municipal institution owned and operated by the City of Cleveland. It was founded in 1837 and first occupied its Scranton Road site in 1855. The present hospital group, constructed largely since 1922, covers twenty-seven acres and includes sixteen buildings with facilities for the care of 1,650 patients. The General Building (722 beds) houses the medical and surgical services, pediatrics, obstetrics, electrocardiography, and x-ray. There are, in addition, separate buildings for Contagious Diseases (200 beds), Tuberculosis (350 beds), Psychopathic Diseases (307 beds), Pathology, and the Out-Patient Department.



Top: Cleveland Museum of Art.

Center: Severance Hall (Home of Cleveland's Symphony Orchestra).

Foot: Cleveland's Public Auditorium. A unit in Cleveland's Lake Front development, it is one of a group of structures including The Court House, The City Hall, The Board of Education Headquarters, and the Municipal Stadium.

City Hospital is affiliated with Western Reserve University and is a teaching unit of the Medical School. Since 1913 the University has assumed responsibility for the professional care of patients. Visiting staff members are nominated by the faculty of the School of Medicine. In this way it has been possible to assure patients scientific treatment and to carry on medical teaching undisturbed by the political contingencies of changing city administrations. The present professional staff comprises 106 attending physicians, 95 house physicians, and 615 nurses.

In addition to University and City hospitals, medical students receive clinical instruction at Charity Hospital which was a pioneer institution dating from the Civil War period and remains as the only downtown hospital in Cleveland. It has a capacity of 300 beds and is located on East 22nd Street four blocks south of Euclid Avenue. It has very important out-patient and emergency departments.

St. Luke's Hospital is a general hospital affiliated with the Methodist Episcopal Church and has a capacity of 391 beds to be expanded ultimately to 500 beds. It is beautifully located at the entrance to Shaker Heights, residential suburb of the city of Cleveland. The building was constructed in 1927 and occupies a spacious tract of sixteen and a half acres on Shaker Boulevard at East 115th Street on the Rapid Transit Railroad. The institution, representing a value of approximately \$8,000,000, is one of the largest privately endowed institutions in the country. It was made possible by the gift of Mrs. Frances F. Prentiss as a memorial building in honor of Dr. Dudley P. Allen. The hospital provides complete professional service under the three main divisions of medicine, surgery and obstetrics, with a large and well developed department of pathology.

Mount Sinai Hospital, 1800 East 105th Street, is a non-sectarian hospital founded in 1916. The present capacity of the hospital is 270 beds and comprises complete facilities for general medical and surgical services and their sub-specialties. The hospital was enlarged in 1926 by the addition of a separate out-patient department building, a nurses' home, and laboratory for pathology. The professional staff comprises 120 attending physicians and 18 house physicians. Served annually are 7,500 in-patients, 3,000 emergency patients, and 10,000 clinic patients. The hospital maintains a nurses' training school.

The Cleveland Clinic is located at Euclid Avenue and East 93rd Street. The Cleveland Clinic Foundation was organized by Dr. Frank E. Bunts, Dr. George Crile, Dr. William E. Lower and Dr. John Phillips in February, 1921, under a charter from the State of Ohio. The Cleveland Clinic Building was opened on February 26, 1921. As the activities of the Clinic expanded and the interests of the Foundation broadened, other buildings were added, the Cleveland Clinic Hospital with 225 beds in 1924, the Power Plant and Laundry in 1926, the Research Building in 1928, the new Clinic Building in 1931. The buildings house Museums of Pathology, of Intelli-

gence, Power and Personality of Man and Animals, and of Comparative Anatomy and Physiology.

St. Alexis Hospital is located in the steel mill district on the corner of Broadway and McBride Street. It is one of the city's older hospitals, dating from 1884 and has a capacity of 220 beds. It renders invaluable service to the employees of the American Steel and Wire Company, the Republic, Ohio and other Steel Companies. All general hospital services are provided except obstetrics. The staff consists of 38 visitants and 16 interns and residents.

The Cleveland Museum of Health and Hygiene, the first of its kind to be incorporated in the United States, has 521 physician members and a suitable building which should be ready for opening in 1940.

The following hospitals with locations and bed capacities are indicated for the convenience of the members of the College of Physicians. No formal demonstrations will be given, but any member desiring to visit the institutions will be welcomed.

Huron Road Hospital, 13921 Terrace Road, East Cleveland .....	256 beds
U. S. Marine Hospital under the U. S. Public Health Service, East 124th Street and Fairhill Road .....	303 beds
Glenville Hospital, 701 Parkwood Drive, North East .....	110 beds
Cleveland State Hospital for the Insane, Turney Road, South Side (100 acre tract of land) .....	2300 beds

A group of West Side hospitals with their respective capacities follows:

St. John's Hospital, 7911 Detroit .....	217 beds
Fairview Park Hospital, 3305 Franklin Boulevard .....	200 beds
Lakewood City Hospital, 14519 Detroit .....	176 beds
Evangelical Deaconess Hospital, 4233 Pearl Road .....	144 beds
Lutheran Hospital, 2609 Franklin Avenue .....	137 beds
Grace Hospital, 2307 West 14th Street .....	80 beds

### *The Convention Hall*

The general sessions of the College of Physicians will be held in the Public Auditorium. This is one of the first structures of its kind, built at a cost of \$15,000,000. Its range of service is practically unlimited. Sixteen events can be held simultaneously and without interference. The Main Auditorium seats 12,500 persons and can be readily adapted for the sessions of a huge convention. The beautiful Music Hall seats 3,000 and is well adapted to the needs of the College. The Ball Room and Little Theatre have seating capacities of 1,500 and 700 respectively; and ten other halls range in seating capacity from 90 to 500. A common stage makes it possible for the Main Auditorium and the Music Hall to seat 16,000 persons for a single event. The building is of fireproof construction and designed in Italian Renaissance architecture. The color and the diffused lighting in the main auditorium lend a warmth and softness unusual in buildings of such immense proportions. The Auditorium's acoustics have been declared perfect. The \$100,000 pipe organ is one of the finest in America. Among other features



of the building are spacious lobbies and corridors, wide ramps and stairways, committee rooms, lockers, telephone booths, women's and men's retiring rooms, emergency hospital, checkroom and telegraph stations. The Hall is ideally located in the heart of the downtown district within easy walking distance of all principal hotels and shops.

The best testimonial as to the adequacy of Cleveland's convention facilities is the frequency with which the country's largest conventions and trade expositions return to this city. With half the population of the United States and Canada living within an overnight's ride, maximum attendance is a regular report at Cleveland conventions. All air and water schedules are synchronized with railroad schedules to and from all important centers so that your journey always requires the minimum of time and effort.

Cleveland's hotel accommodations for its many convention visitors are splendid. Six hotels alone have 4500 rooms—each with private bath. Designed for conventions, modern and well equipped, these hotels assist materially in making Cleveland conventions successful. Numerous assembly, banquet and conference rooms are always available. An important feature in the larger hotels is the location of the meeting rooms. None of these is located higher than the mezzanine floor, relieving the convention visitor of the annoyance of congestion at elevators.

Cleveland is expecting a record attendance at the 1940 Session of the College of Physicians. Western Reserve Medical School, the hospitals and the officers of the college are planning a program that will be in keeping with record attendance and the traditions of Cleveland medicine.

# ANNALS OF INTERNAL MEDICINE

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## SPECIFIC TREATMENT OF THE PNEUMOCOCCIC PNEUMONIAS; AN ANALYSIS OF THE RESULTS OF SERUM THERAPY AND CHEMOTHERAPY AT THE BOSTON CITY HOSPITAL FROM JULY 1938 THROUGH JUNE 1939 \*

By MAXWELL FINLAND, F.A.C.P., WILLIAM C. SPRING, JR., and FRANCIS  
C. LOWELL, *Boston, Massachusetts*

DURING the past few months, in accord with the general trend in the treatment of bacterial infections, the focus of attention in the literature dealing with the therapy of pneumonia has shifted from specific serums to chemotherapy. This was quite natural and is easy to appreciate in a disease like pneumonia, where specific serotherapy is rather laborious, expensive and subject to a number of important limitations, in contrast to chemotherapy, which is simple to administer, relatively inexpensive and has a wider scope of usefulness. The generally favorable results more or less universally obtained with sulfapyridine have fully justified this shift in emphasis. Nevertheless, the fact that specific antipneumococcic serums, within their limitations, are highly effective in radically reducing the death rate and curtailing the acute disease in cases of pneumococcic pneumonia is now attested by a wide experience perhaps as thoroughly controlled as any therapy can be in such a disease. Furthermore, recent results with serotherapy have shown steady improvement with its extension to include more types of pneumococci, and particularly with the introduction of rabbit serums which have proved highly effective against infections with the common pneumococcus types other than Type III.<sup>1</sup> Adequate data are not yet available for the proper evaluation of the relative merits of the newer chemotherapeutic agents and the recent serums, nor is it possible as yet to delineate the scope of usefulness of these agents when given separately or in combination.

In this paper we wish to present an analysis of the results of serotherapy

\* Received for publication January 2, 1940.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

and chemotherapy in pneumococcic pneumonia in adults as carried out at the Boston City Hospital during the 1938 to 1939 season. This experience is of especial interest since (1) serums and chemicals were used separately and in combination; (2) all of the cases admitted to the hospital that received neither of these forms of therapy are also included; and (3) similar data accumulated under more or less comparable conditions over a number of years in the same hospital are available for comparison.<sup>2</sup> Although the number of cases included may appear at first glance to be large, so many factors require close scrutiny that only the more important ones involved in the proper evaluation of the present therapy can receive adequate attention.

#### PATIENTS, MATERIALS AND METHODS

The patients included in this study were admitted to the Boston City Hospital between July 1, 1938 and June 30, 1939. They were all over 12 years of age, each had an acute respiratory infection with consolidation in the lung, demonstrated in almost every instance either by roentgenogram or at necropsy, and pneumococci were identified and typed on one or more occasions from sputum and/or other sources such as blood, lung or purulent exudates.

The diagnostic typing serums, most of the therapeutic serums and the bulk of the sulfapyridine were supplied through the generosity of the Lederle Laboratories, Inc. Therapeutic horse serums were also furnished by the Antitoxin and Vaccine Laboratory of the Massachusetts Department of Public Health, some of the therapeutic rabbit serums by the Squibb Laboratories and part of the sulfapyridine supply by Merck and Company and Calco Chemical Company. Sulfapyridine became available to us during the latter part of October, and the supply of this drug was limited at first. All of the lots of therapeutic serums were refined and concentrated, and, for the most part, were supplied for clinical trial prior to their release for general use.

No attempt was made to carry out a controlled therapeutic experiment, since previous experience has convinced us that in such a highly fatal disease strict alternation of any sort is impractical and, indeed, grossly misleading when agents with known lifesaving properties are available. In general, sulfapyridine was first used alone in relatively mild cases, when multiple "higher" types were found, in cases in which potent serums were not available or where no striking benefits were to be expected from them. Treatment with this drug was begun simultaneously with specific serum therapy in cases with the poorest prognoses, and the two agents were used in sequence when the response to one or the other seemed inadequate or when severe untoward symptoms were encountered from one of them. The use of the drug was gradually extended, so that in the latter part of the season most patients who were acutely ill were given sulfapyridine as soon as the clinical diagnosis was made, but only after sputum was obtained for typing and blood for culture. Serum was then given to some of the severest cases

as soon as the type was obtained, and to others as soon as it was felt that response to the drug was not satisfactory or when severe untoward reactions were encountered. Sulfanilamide was used in a number of cases, particularly in the first half of the season, in more or less the same manner as during the previous year.<sup>2</sup>

A large number of cases are included that received neither serum nor sulfapyridine.\* For the most part these included: patients whose illness appeared mild and who recovered spontaneously; those who, when the bacteriological diagnosis was made, had already died or had shown sufficient improvement so that no specific therapy was required; a number in whom the pneumonia complicated other diseases which obscured the signs and symptoms; and, finally, some cases with atypical signs, symptoms and course. Actually the choice of cases for therapy is much better judged in retrospect and will be brought out in the analysis which follows.

#### ANALYSIS OF THE CASES AND OF THE RESULTS OF THERAPY

Proper appreciation of the full value and limitations of any therapeutic agent in the treatment of pneumonia requires a careful analysis of the important factors in the host and in the infection which influence the prognosis, as well as the factors concerning the remedy used and its untoward effects. These will be considered in as much detail as the volume of data seems to warrant. As far as possible, the data will be presented in tabular form so as to permit comparisons of the various forms of therapy. For the sake of brevity, these data will only be summarized in the text and such facts will be brought out as are not directly apparent from the tables. Sulfanilamide was used in the treatment of a number of the cases which are included among those who received serum and among those who received neither serum nor sulfapyridine. To avoid confusion, the effects of sulfanilamide will not be noted in all the tables, but will be considered in a separate section.

TABLE I

Gross Mortality Rates—Pneumococcic Pneumonia—Boston City Hospital, 1938-1939

Therapy	No. of Cases	Died	Per cent Died
Specific serum	211	28	13.3
Serum and sulfapyridine	129	31	24.0
Sulfapyridine	225	40	17.8
No serum, no sulfapyridine *	472	135	28.6
Total	1037	234	22.6

\* Includes 73 cases in which the bacteriological diagnosis was made after death. If these are excluded, there were 399 cases with 62 deaths, or 15.5 per cent.

*Gross Fatality.* These figures are shown in table 1. Several significant points may be mentioned, since they will not appear in the tables.

\* These cases will be referred to as "untreated" and all the others will be referred to as specifically treated. Those who received sulfanilamide alone are included among the "untreated" cases.

"Specific treatment," which for the pneumococcic pneumonias can now be considered to include serum or sulfapyridine or both, was used during this year in 565, or 54 per cent of the 1037 cases. Among these 565 treated cases there were 99 deaths, or 17.5 per cent. In the seven years prior to July 1936, there were 2648 cases of pneumococcic pneumonia, of which 470, or 16.5 per cent, were treated with specific serums; among the latter, 19 per cent died. In these seven years, 43 per cent of all the cases died, as compared with 22.6 per cent during 1938 to 1939. In other words, although the reduction in death rate among specifically treated cases was slight (from 19 to 17.5 per cent), the total death rate among all the adult cases of pneumococcic pneumonia was reduced to about one-half, due largely to the extension of treatment to a considerably greater proportion of the severe cases. In the two intervening years, as already pointed out,<sup>2</sup> serum treatment was being extended by the inclusion of cases treated late in the disease and also cases due to additional pneumococcus types for which serums became available. The greatest extension of treatment, however, occurred in the 1938 to 1939 season with the introduction of sulfapyridine and the increased availability of rabbit serums. That the residue of cases treated without serum or drugs during 1938 to 1939 includes a greater proportion of milder cases than in previous years is indicated by the death rate of 28.6 per cent in this group, as compared with 45 per cent in the non-serum treated cases prior to July 1936, and about 40 per cent in similar cases due to the common types of pneumococci during the following two years.<sup>2</sup> The incidence of bacteremia was also considerably lower in the untreated cases during 1938 to 1939.

*Monthly Variations.* The death rates shown in table 1 are essentially the same as those given in our preliminary report, which included the cases treated prior to March 15 of the same season.<sup>3</sup> The present report includes more than twice as many recipients of sulfapyridine. The numbers of cases treated each month are shown in table 2. Only a small proportion of cases received sulfapyridine during October and November, about one-third of all the cases received the drug during the following two months and about one-half of all the patients were given the chemical during February and thereafter. There were wide fluctuations in proportion of deaths from month to month, the variations being greatly exaggerated because of the relatively small numbers involved. There was no obvious correlation, however, between the proportion of cases receiving the different kinds of therapy and the death rates in each group.

*Types of Pneumococci (Table 3).* Here we begin to observe the first important differences in the selection of cases for the various forms of therapy. Types I, II, IV, V, VII and VIII which, excluding Type III, are the six most frequent types in the pneumonia of adults, are also the types which are most regularly associated with typical and primary lobar pneumonia.<sup>2a</sup> These six types represented 84, 78, 51 and 23 per cent, respectively, of the cases treated with serum alone, serum and sulfapyridine,

sulfapyridine and neither agent. Among the cases of these types, the mortality rates for the four groups, in the same order, were 12, 22, 13 and 31 per cent.

TABLE II

Distribution of Cases According to the Month During Which the Patients Were Admitted to the Hospital

Month	Specific Serum		Serum and Sulfapyridine		Sulfapyridine		No Serum, No Sulfapyridine		All Cases	
	Number	Died	Number	Died	Number	Died	Number	Died	Number	Died
<i>1938</i>										
July	7 <sup>3</sup>	0	0	—	0	—	17 <sup>1</sup>	6 <sup>1</sup>	24 <sup>4</sup>	6 <sup>1</sup>
August	11 <sup>4</sup>	4 <sup>3</sup>	0	—	0	—	33 <sup>2</sup>	14 <sup>2</sup>	44 <sup>6</sup>	18 <sup>5</sup>
September	14 <sup>5</sup>	4 <sup>4</sup>	0	—	0	—	23	10	37 <sup>5</sup>	14 <sup>4</sup>
October	29 <sup>6</sup>	3 <sup>2</sup>	2 <sup>1</sup>	1 <sup>1</sup>	1	1	41 <sup>7</sup>	8 <sup>5</sup>	73 <sup>14</sup>	13 <sup>8</sup>
November	21 <sup>4</sup>	4 <sup>1</sup>	7 <sup>3</sup>	3 <sup>3</sup>	3	0	38	9	69 <sup>7</sup>	16 <sup>4</sup>
December	24 <sup>5</sup>	0	23 <sup>11</sup>	4 <sup>4</sup>	8 <sup>1</sup>	2	55 <sup>2</sup>	14 <sup>2</sup>	110 <sup>19</sup>	20 <sup>5</sup>
<i>1939</i>										
January	38 <sup>14</sup>	5 <sup>5</sup>	28 <sup>16</sup>	9 <sup>6</sup>	20 <sup>3</sup>	7 <sup>3</sup>	54 <sup>4</sup>	17 <sup>4</sup>	140 <sup>37</sup>	38 <sup>18</sup>
February	10 <sup>3</sup>	1 <sup>1</sup>	16 <sup>7</sup>	2 <sup>2</sup>	45 <sup>10</sup>	8 <sup>3</sup>	67 <sup>3</sup>	12 <sup>2</sup>	138 <sup>23</sup>	23 <sup>8</sup>
March	15 <sup>7</sup>	3 <sup>2</sup>	20 <sup>13</sup>	6 <sup>6</sup>	53 <sup>15</sup>	5 <sup>3</sup>	57 <sup>5</sup>	18 <sup>5</sup>	145 <sup>40</sup>	32 <sup>15</sup>
April	21 <sup>5</sup>	3 <sup>2</sup>	23 <sup>17</sup>	4 <sup>4</sup>	36 <sup>8</sup>	6 <sup>4</sup>	45 <sup>3</sup>	12 <sup>3</sup>	125 <sup>33</sup>	25 <sup>13</sup>
May	18 <sup>2</sup>	0	8 <sup>4</sup>	1 <sup>1</sup>	43 <sup>11</sup>	7 <sup>4</sup>	24 <sup>1</sup>	6 <sup>1</sup>	93 <sup>18</sup>	14 <sup>6</sup>
June	3 <sup>1</sup>	1 <sup>1</sup>	2 <sup>2</sup>	1 <sup>1</sup>	16 <sup>3</sup>	4 <sup>2</sup>	18 <sup>2</sup>	9 <sup>2</sup>	39 <sup>8</sup>	15 <sup>6</sup>
Totals	211 <sup>59</sup>	28 <sup>21</sup>	129 <sup>74</sup>	31 <sup>23</sup>	225 <sup>51</sup>	40 <sup>19</sup>	472 <sup>30</sup>	135 <sup>27</sup>	1037 <sup>214</sup>	234 <sup>95</sup>

Superscripts represent numbers of patients with pneumococcus bacteremia.

The patients in whom the onset of the disease occurred in the hospital are listed according to the time of onset.

The Type III cases are of especial interest. Eighty cases due to this type were treated with serum or sulfapyridine, or both, with 15 deaths (19 per cent), as compared with 21 deaths, or 33 per cent, of the 63 who received no specific treatment. Prior to July 1936, the mortality in this type over a seven-year period was 60 per cent, and during the next two years it was 47 per cent in untreated cases and 43 per cent among 67 cases treated with serum or sulfanilamide, or both.<sup>2e</sup> However, bacteremia was less frequent in the present cases; only 15 of the treated cases (19 per cent) and 5 of those not treated specifically (8 per cent) had positive cultures, as compared with a 36 per cent bacteremic incidence prior to 1936 and 26 per cent in the two intervening years. It is significant, nevertheless, that six bacteremic Type III cases recovered following treatment during this year. All of these six cases received sulfapyridine and only one received serum in addition.

Among the so-called "higher" types, comparisons are difficult since serums were used only in the severest cases. This is indicated by the high incidence of bacteremia in those receiving serum, particularly where it was used to supplement sulfapyridine therapy.

TABLE III

Distribution of Cases and Deaths According to Pneumococcus Types

Type	Specific Serum		Serum and Sulfapyridine		Sulfapyridine		No Serum, No Sulfapyridine		All Cases	
	No.	Died	No.	Died	No.	Died	No.	Died *	No.	Died
I	69 <sup>14</sup>	5 <sup>4</sup>	54 <sup>38</sup>	14 <sup>13</sup>	58 <sup>25</sup>	8 <sup>7</sup>	16 <sup>2</sup>	4 <sup>2</sup> (4)	197 <sup>79</sup>	31 <sup>26</sup>
II	29 <sup>11</sup>	7 <sup>4</sup>	22 <sup>12</sup>	4 <sup>4</sup>	8 <sup>3</sup>	2 <sup>2</sup>	10 <sup>3</sup>	2 <sup>2</sup> (1)	69 <sup>29</sup>	15 <sup>12</sup>
III	11 <sup>3</sup>	3 <sup>3</sup>	19 <sup>3</sup>	3 <sup>2</sup>	50 <sup>9</sup>	9 <sup>4</sup>	63 <sup>6</sup>	21 <sup>5</sup> (9)	143 <sup>20</sup>	36 <sup>14</sup>
IV	11 <sup>2†</sup>	0	3 <sup>2</sup>	1 <sup>1</sup>	7 <sup>3</sup>	2 <sup>2</sup>	16 <sup>2</sup>	6 <sup>2</sup> (3)	37 <sup>9</sup>	9 <sup>5</sup>
V	20 <sup>7</sup>	5 <sup>5</sup>	9 <sup>5</sup>	0	12 <sup>2</sup>	1 <sup>1</sup>	11 <sup>3</sup>	7 <sup>3</sup> (4)	52 <sup>17</sup>	13 <sup>9</sup>
VI	4	0	—	—	5	1	28 <sup>1</sup>	7 <sup>1</sup> (5)	37 <sup>1</sup>	8 <sup>1</sup>
VII	24 <sup>5</sup>	3 <sup>2</sup>	7 <sup>4</sup>	1 <sup>1</sup>	15 <sup>1</sup>	0	20 <sup>1</sup>	2 (2)	66 <sup>11</sup>	6 <sup>3</sup>
VIII	24 <sup>7</sup>	1 <sup>1</sup>	6 <sup>2</sup>	2 <sup>1</sup>	14 <sup>1</sup>	2	35 <sup>2</sup>	12 <sup>2</sup> (4)	79 <sup>12</sup>	17 <sup>4</sup>
IX	2 <sup>1</sup>	0	—	—	7	0	32 <sup>2</sup>	9 <sup>2</sup> (3)	41 <sup>3</sup>	9 <sup>2</sup>
X	1 <sup>1</sup>	0	—	—	1	0	20 <sup>1</sup>	4 <sup>1</sup> (2)	22 <sup>2</sup>	4 <sup>1</sup>
XI	1	1	—	—	5	2	17 <sup>1</sup>	3 <sup>1</sup>	23 <sup>1</sup>	6 <sup>1</sup>
XII	2 <sup>1</sup>	0	—	—	2 <sup>1</sup>	1 <sup>1</sup>	11 <sup>1</sup>	2	15 <sup>3</sup>	3 <sup>1</sup>
XIII	—	—	—	—	1	0	15	1 (1)	16	1
XIV	3 <sup>2</sup>	0	2 <sup>1</sup>	1 <sup>1</sup>	8 <sup>3</sup>	3 <sup>2</sup>	8 <sup>1</sup>	3 <sup>1</sup> (1)	21 <sup>7</sup>	7 <sup>4</sup>
XV	1 <sup>1</sup>	1 <sup>1</sup>	—	—	2	1	8	1 (1)	11 <sup>1</sup>	3 <sup>1</sup>
XVI	—	—	1 <sup>1</sup>	1 <sup>1</sup>	2	0	8	0	11 <sup>1</sup>	1 <sup>1</sup>
XVII	—	—	1 <sup>1</sup>	0	3	1	18 <sup>1</sup>	10 <sup>1</sup> (5)	22 <sup>2</sup>	11 <sup>1</sup>
XVIII	4 <sup>1</sup>	1	—	—	8 <sup>1</sup>	3	20 <sup>2</sup>	3 <sup>2</sup> (2)	32 <sup>4</sup>	7 <sup>2</sup>
XIX	2 <sup>2</sup>	0	2 <sup>2</sup>	1 <sup>1</sup>	5	1	23 <sup>1</sup>	8 <sup>1</sup> (6)	32 <sup>5</sup>	10 <sup>2</sup>
XX	—	—	1 <sup>1†</sup>	1 <sup>1</sup>	2 <sup>1</sup>	0	16	8 (6)	19 <sup>2</sup>	9 <sup>1</sup>
XXI	—	—	—	—	1 <sup>1</sup>	0	7	2 (2)	8 <sup>1</sup>	2
XXII	1	0	—	—	3	2	11	1	15	3
XXIII	—	—	1 <sup>1</sup>	1 <sup>1</sup>	2	1	11	5 (4)	14 <sup>1</sup>	7 <sup>1</sup>
XXIV	—	—	—	—	—	—	7	3 (1)	7	3
XXV	1 <sup>1</sup>	1 <sup>1</sup>	1 <sup>1</sup>	1 <sup>1</sup>	—	—	4	1 (1)	6 <sup>2</sup>	3 <sup>2</sup>
XXVII	1	0	—	—	—	—	3	1	4	1
XXVIII	—	—	—	—	—	—	5	2 (2)	5	2
XXIX	—	—	—	—	2	0	20 <sup>1</sup>	6 <sup>1</sup> (3)	22 <sup>1</sup>	6 <sup>1</sup>
XXXI	—	—	—	—	2	0	4	1 (1)	6	1
Not I-XXXII	—	—	—	—	—	—	5§	0	5	0
Total	211 <sup>59</sup>	28 <sup>21</sup>	129 <sup>74</sup>	31 <sup>28</sup>	225 <sup>51</sup>	40 <sup>19</sup>	472 <sup>30</sup>	135 <sup>27</sup> (73)	1037 <sup>214</sup>	234 <sup>95</sup>

Superscripts represent numbers of patients with pneumococcic bacteremia.

\* Parentheses enclose numbers of cases in which the bacteriological diagnosis was made after death.

† One case had Type XX in addition and received serum for both types.

‡ Types VI and XX in blood cultures in this case.

§ 4 of these cases had a pneumococcus that reacted with Types XI and XVI serums.<sup>8</sup>

*Incidence of Bacteremia and Effect on Mortality (Table 4).* Bacteremia was demonstrated before treatment in 184, or 32.6 per cent of the 565 specifically treated cases. This was about four and one-half times as frequent as among the untreated cases. Among the patients treated with both serum and sulfapyridine it was more than twice as frequent as among those treated with either agent alone. This would indicate that, from the point of view of the pneumococcic infection in the lung, a severer and more typical group of cases was chosen for specific treatment, and the worst of these received both serum and drug. As in all our previous reports, the

TABLE IV

Mortality in Relation to Results of Blood Cultures  
Pneumococcic Pneumonia—Boston City Hospital 1938–1939

Therapy	Cases with Positive Blood Cultures			Per cent Positive	Cases with Negative Blood Cultures		
	No. of Cases	Died	Per cent Died		No. of Cases	Died	Per cent Died
Specific serum	59	21	35.6	28.0	152	7	4.6
Serum and sulfapyridine	74	28	37.8	57.4	55	3	5.5
Sulfapyridine	51	19	37.2	22.7	174	21	12.1
No serum, no sulfapyridine *	30	27	90.0	7.3	380	96	25.3
Total	214	95	44.4	21.9	761	127	16.7

\* In 16 of the bacteremic cases and in 53 of the non-bacteremic cases, the bacteriological diagnosis was made after death. No blood cultures were made in 62 cases of this group, of whom 12 died (19.4 per cent).

TABLE V

Qualitative Variations in the Results of Blood Cultures in Relation to Specific Serum and/or Sulfapyridine Therapy 1938–39

	Serum		Serum and Sulfapyridine		Sulfapyridine		Serum and/or Sulfapyridine	
	No.	Died	No.	Died	No.	Died	No.	Died
Results of multiple cultures made before treatment								
First positive, then negative	4	0	7	1	8	1	19	2
First negative, then positive	11	4	12	2	4	0	27	6
All positive	20	8	35	15	16	8	71	31
Blood cultures negative before treatment and positive after treatment	1	1	2	2	6	2	9	5
Blood cultures positive before treatment								
Positive after treatment	8	6	20	9	12	7	40	22
Negative after, then positive again	2	2	3	3	1	0	6	5
Negative after treatment (fatal)	—	8	—	16	—	9	—	33

Only blood cultures yielding growth of pneumococci are listed here as positive. *Hemolytic streptococci* were obtained in blood cultures taken after therapy from 10 patients, as follows:

Serum treated—4 bacteremic (pneumococcus) cases and 1 non-bacteremic case; one of the former recovered, all the others died.

Serum and sulfapyridine—4 bacteremic patients, of whom 2 died.

Sulfapyridine—1 non-bacteremic patient, who recovered.



mortality among bacteremic cases was three or more times as great as in non-bacteremic cases, regardless of the kind of treatment used.

The variations that were noted in the results of blood cultures taken during the acute disease in relation to therapy are summarized in table 5. There were 19 patients in whom the blood culture taken just before treatment was begun was sterile, although previous cultures were positive for pneumococci. Only two of these patients died. In a somewhat larger number of cases the reverse was true—the culture taken just prior to treatment was positive, whereas previous cultures were negative. There were six deaths among 27 such patients. All the six fatal cases received serum and two of them also received sulfapyridine. The mortality was considerably higher when multiple cultures taken before treatment were all positive, and this was true regardless of the therapy given.

Of especial interest are the nine patients in whom the first positive blood culture was obtained after treatment was begun, although cultures taken before treatment were all sterile. The one case that received serum alone had Type III pneumococcic pneumonia and delirium tremens. Cultures of blood taken on two occasions before treatment was begun were sterile, but a third one obtained 12 hours after 80,000 units of Type III serum had been given yielded 550 colonies per cubic centimeter of blood. In the meantime the patient had developed increasing "collapse," although there were no obvious reactions in relation to therapy. One of the patients who received serum followed by sulfapyridine had persistently positive cultures for Type I pneumococcus after treatment. He had thrombophlebitis, pyarthrosis and probably endocarditis. In the seven remaining patients the first positive blood culture was obtained from 8 to 20 hours after sulfapyridine therapy was started. The one patient among them who received serum in addition subsequently had sterile cultures, but he succumbed to a cranial lesion which preceded the onset of his pneumonia.

The mortality was particularly high among those bacteremic patients in whom the blood stream was not rapidly sterilized following therapy, that is, if any of the blood cultures taken after the beginning of treatment were still positive. This was true regardless of whether serum or drug, or both, were used. The five serum recipients, including three who received sulfapyridine in addition, whose blood streams were only temporarily sterilized following treatment, all had bacterial endocarditis. In a considerable number of bacteremic patients, death occurred in spite of repeatedly negative blood cultures following therapy, even including the heart's blood in those who came to autopsy. Many of them died with purulent focal complications. It is of interest that 8 of the 10 treated patients who had superinfections with hemolytic streptococci had pneumococcus bacteremia before treatment.

One patient treated late in the disease had a positive blood culture for Type XX pneumococcus before therapy. Following the administration of Type XX antipneumococcus rabbit serum and sulfapyridine, sterile blood

cultures were obtained. Cultures taken on the fourth day after sulfapyridine was discontinued and later were again positive, and these all showed both Type XX and Type VI pneumococci. Both these types were also obtained from cultures of endocardial vegetations found at autopsy.

Quantitative blood cultures in agar pour plates were made in about one-half of the bacteremic cases. The results are summarized in table 6. As

TABLE VI  
Summary of Results of Quantitative Blood Cultures in Bacteremic Cases

Number of Colonies per c.c. of Blood	Serum Treated		Serum and Sulfapyridine		Sulfapyridine		All Treated Cases	
	Number	Died	Number	Died	Number	Died	Number	Died
0*	4	0	6	1	4	0	14	1
1-25	12	7	18	3	7	2	37	12
26-100	5	3	7	1	5	3	17	7
100+	3	3	13	10	8	8	24	21
Total	24	13	44	15	24	13	92	41

\* Broth cultures positive, no growth in agar pour plate with 1 and 2 c.c. of blood.

was to be expected, the mortality was greatest among those patients whose blood yielded a growth of large numbers of pneumococci. The only three patients who recovered during this year when more than 100 colonies per cubic centimeter of blood were found before treatment all received both serum and sulfapyridine. Their cultures yielded 550, 400 and 149 colonies, respectively. The one with the 550 colonies was a woman of 69 who recovered without complications of the pneumonia, although she sustained a Colles's fracture and facial injury after falling out of bed while still under treatment. The other two patients both developed empyema; the one with 400 colonies recovered following repeated thoracenteses without operation and the other recovered following closed thoracotomy.

*Effect of Age.* From table 7 it is apparent that most of the older patients were treated with sulfapyridine by choice. This was due, in part, to the greater proportion of cases due to Type III and to the "higher" types, and in part to the fact that very favorable results had not been obtained in the older age groups in previous years. The severest among these patients received serum, in addition. Considering that two-thirds of the patients over 60 years of age who were treated with both serum and sulfapyridine had positive blood cultures, the death rate of less than 30 per cent in 37 such cases is remarkable. Only about one-fourth of the 62 patients over 60 years old and treated with sulfapyridine alone had positive blood cultures, and the mortality was 30 per cent. This is far better than previous death rates in this age group obtained with other kinds of therapy, including specific serums. The number of patients over 60 who were treated with

TABLE VII  
Mortality in Relation to Age

Age Group (years)	Therapy														
	Specific Serum			Serum and Sulfapyridine			Sulfapyridine			No Serum, No Sulfapyridine			All Cases		
	No.	Died	%	No.	Died	%	No.	Died	%	No.	Died	%	No.	Died	%
13-19*	31 <sup>6</sup>	1 <sup>1</sup>	3	5 <sup>5</sup>	3 <sup>3</sup>	60	23 <sup>2</sup>	1	4	42	1	2	101 <sup>13</sup>	6 <sup>4</sup>	5.9
20-29	41 <sup>10</sup>	1 <sup>1</sup>	2	12 <sup>3</sup>	0	0	24 <sup>4</sup>	4 <sup>1</sup>	17	75 <sup>2</sup>	5 <sup>1</sup>	7	152 <sup>19</sup>	10 <sup>3</sup>	6.6
30-39	57 <sup>14</sup>	6 <sup>3</sup>	11	25 <sup>15</sup>	6 <sup>0</sup>	24	32 <sup>8</sup>	5 <sup>1</sup>	16	60 <sup>3</sup>	9 <sup>3</sup>	15	174 <sup>40</sup>	26 <sup>13</sup>	14.9
40-49	36 <sup>12</sup>	7 <sup>6</sup>	19	25 <sup>16</sup>	7 <sup>7</sup>	28	47 <sup>15</sup>	6 <sup>4</sup>	13	87 <sup>4</sup>	12 <sup>3</sup>	14	195 <sup>47</sup>	32 <sup>20</sup>	16.9
50-59	31 <sup>10</sup>	6 <sup>5</sup>	19	25 <sup>11</sup>	5 <sup>3</sup>	20	37 <sup>7</sup>	6 <sup>3</sup>	16	66 <sup>5</sup>	24 <sup>4</sup>	36	159 <sup>33</sup>	41 <sup>15</sup>	27.2
60-69	12 <sup>0</sup>	6 <sup>4</sup>	50	26 <sup>16</sup>	6 <sup>5</sup>	23	36 <sup>8</sup>	8 <sup>5</sup>	22	70 <sup>8</sup>	35 <sup>8</sup>	50	144 <sup>38</sup>	55 <sup>22</sup>	38.2
70+	3 <sup>1</sup>	1 <sup>1</sup>	33	11 <sup>8</sup>	4 <sup>4</sup>	36	26 <sup>7</sup>	10 <sup>5</sup>	38	72 <sup>8</sup>	49 <sup>8</sup>	68	112 <sup>24</sup>	64 <sup>18</sup>	57.1
Total	211 <sup>59</sup>	28 <sup>21</sup>	13	129 <sup>74</sup>	31 <sup>28</sup>	24	225 <sup>51</sup>	40 <sup>19</sup>	18	472 <sup>30</sup>	135 <sup>27</sup>	29	1037 <sup>214</sup>	234 <sup>95</sup>	22.6

\* Superscripts represent numbers of bacteremic cases.

serum alone is too small for comparison. These represented more typical cases than those receiving sulfapyridine alone; almost all were due to the common types. The incidence of bacteremia among them was higher, as was also the death rate. Obviously the best results in the older age groups were obtained with the combination of serum and sulfapyridine. Among the younger patients, the apparently higher death rates with the combination therapy were obviously due to the inclusion in this group of the severest

TABLE VIII  
Mortality in Relation to the Duration of the Disease When Treatment Was Begun

Day Treatment Begun *	Therapy														
	Specific Serum			Serum and Sulfapyridine			Sulfapyridine			No Serum, No Sulfapyridine			All Cases		
	No.	Died	%	No.	Died	%	No.	Died	%	No.	Died	%	No.	Died	%
Third or earlier	91 <sup>21</sup>	5 <sup>3</sup>	5	47 <sup>19</sup>	6 <sup>5</sup>	13	62 <sup>13</sup>	7 <sup>4</sup>	11	242 <sup>12</sup>	69 <sup>10</sup>	32	442 <sup>65</sup>	87 <sup>22</sup>	19.5
Fourth	40 <sup>11</sup>	4 <sup>3</sup>	10	14 <sup>5</sup>	1 <sup>1</sup>	7	42 <sup>11</sup>	5 <sup>3</sup>	12	40 <sup>2</sup>	4 <sup>2</sup>	10	136 <sup>29</sup>	14 <sup>9</sup>	10.3
Fifth	34 <sup>12</sup>	5 <sup>4</sup>	15	23 <sup>17</sup>	6 <sup>6</sup>	26	35 <sup>10</sup>	6 <sup>3</sup>	17	34 <sup>4</sup>	6 <sup>3</sup>	18	126 <sup>43</sup>	23 <sup>16</sup>	18.3
Sixth	24 <sup>5</sup>	8 <sup>5</sup>	33	17 <sup>13</sup>	6 <sup>5</sup>	35	30 <sup>5</sup>	3 <sup>1</sup>	10	20 <sup>1</sup>	2 <sup>1</sup>	10	91 <sup>25</sup>	19 <sup>12</sup>	20.9
Seventh or later†	22 <sup>10</sup>	6 <sup>6</sup>	27	28 <sup>20</sup>	12 <sup>11</sup>	43	56 <sup>11</sup>	19 <sup>8</sup>	34	136 <sup>11</sup>	54 <sup>11</sup>	29	242 <sup>82</sup>	91 <sup>26</sup>	32.6
Total	211 <sup>59</sup>	28 <sup>21</sup>	13	129 <sup>74</sup>	31 <sup>28</sup>	24	225 <sup>51</sup>	40 <sup>19</sup>	18	472 <sup>30</sup>	135 <sup>27</sup>	29	1037 <sup>214</sup>	234 <sup>95</sup>	22.6

\* In the cases receiving neither serum nor sulfapyridine, the day of admission is listed. Superscripts represent numbers of bacteremic cases.

† Including cases with undetermined duration.

cases, many receiving the one agent only after the other was apparently failing to bring about prompt relief.

*Effect of the Time of Beginning Treatment (Table 8).* In accord with previous experience, the death rates in the serum treated cases were lowest in the patients in whom treatment was begun early in the disease. No striking reduction below the expected death rate was noted when serum therapy was first given after the end of the fifth day of illness. This was also true among the patients who received sulfapyridine in addition, since most of the fatal cases listed as having their treatment begun on the fifth day received sulfapyridine alone on that day and were not given serum until the following day, or even later. Among the patients who received sulfapyridine alone, the mortality was high if it was first given after the sixth day, particularly in bacteremic cases. A number of the latter were moribund when treatment was started or they died of complications that had already developed at the time. The lower death rates among those treated earlier with drug alone may be due, in part, to the fact that many severe cases that apparently failed to respond were later given serum and are thus excluded from this category. The high death rate among the patients admitted before the fifth day who received no specific therapy is due, in large part, to the inclusion of many patients whose pneumonia began while they were in the hospital under treatment for other serious illnesses.

The numbers of patients in whom both agents were used are listed in table 9 according to the time relation between the beginning of each kind

TABLE IX  
Effect of Time When Each Treatment Was Begun in Patients Receiving  
Both Serum and Sulfapyridine

	Number of Cases	Bacteremic Cases	Died	Per cent Died
Serum and sulfapyridine begun simultaneously	29	13	4	14
Sulfapyridine given first, followed by serum in:				
Less than 12 hours	38	24	6	16
12 to 18 hours	11	4	2	22
18 to 24 hours	9	7	4	} 41
24 to 48 hours	10	6	4	
More than 48 hours	8	5	3	
Total *	76	46	19	25
Serum given first, followed by sulfapyridine in:				
Less than 12 hours	12	8	3	25
12 to 24 hours	4	3	3	} 42
24 to 48 hours	4	2	1	
More than 48 hours	4	2	1	
Total *	24	15	8	33

\* Only those patients are included in whom it was felt that the acute pulmonary infection was still active when treatment with the second agent was begun.

of therapy. These data would indicate that the combination of serum and sulfapyridine is most effective if both are begun simultaneously or within from 12 to 18 hours of each other.

The effect on mortality of the extent of lung involvement at the time treatment was begun is shown in table 10. Regardless of the kind of

TABLE X  
Mortality in Relation to the Extent of Lung Involvement

Therapy	Pneumonia Involving:						Per cent with More than One Lobe Involved
	One Lobe			More than One Lobe			
	No. of Cases	Died	Per cent Died	No. of Cases	Died	Per cent Died	
Specific serum	158 <sup>42</sup>	12 <sup>9</sup>	7.6	53 <sup>17</sup>	16 <sup>12</sup>	30.2	25.1
Serum and sulfapyridine	54 <sup>32</sup>	9 <sup>8</sup>	16.7	75 <sup>42</sup>	22 <sup>20</sup>	29.3	58.1
Sulfapyridine	152 <sup>27</sup>	11 <sup>6</sup>	7.2	73 <sup>24</sup>	29 <sup>14</sup>	39.7	32.0
No serum, no sulfapyridine	282 <sup>11</sup>	41 <sup>8</sup>	14.5	190 <sup>19</sup>	94 <sup>19</sup>	49.5	40.3
All cases	646 <sup>112</sup>	73 <sup>30</sup>	11.3	391 <sup>102</sup>	161 <sup>65</sup>	41.2	37.7

Superscripts represent the numbers of bacteremic cases.

therapy used, deaths were considerably more frequent when the disease had already extended to involve two or more lobes than when it was still confined to a single lobe at the time when treatment was first given. The difference was much less marked when both serum and sulfapyridine were used than when either was used alone. It is again evident from the large proportion of cases having extensive involvement that more of the worst risks were chosen for treatment with both agents. The death rates were particularly high in the bacteremic cases where more than one lobe was involved. The most favorable results in such cases were obtained with the combination of serum and sulfapyridine. It is noteworthy, also, that among the 33 non-bacteremic cases with more than one lobe involved which were treated with both agents, there were only two deaths (6 per cent), as compared with four deaths (11 per cent) among 36 similar cases treated with serum alone and 15 deaths (31 per cent) among 49 who received only sulfapyridine.

*Atypical (Broncho-) Pneumonias and "Secondary" Pneumonias.* In previous reports <sup>2a</sup> it was pointed out that patients with pneumococcic pneumonia who have atypical pulmonary consolidation (bronchopneumonia) have a higher mortality in spite of a lower incidence of bacteremia than similar patients who, according to the best available evidence, have typical lobar pneumonia. Furthermore, a considerably larger proportion of the atypical pneumococcic pneumonias are secondary to other serious illness,

while the cases of lobar pneumonia are predominantly "primary"; and, conversely, a much larger proportion of the "secondary" cases have atypical lung involvement, while more of the primary pneumonias have typical lobar pneumonia. This was also true in the present cases, as shown in table 11.

TABLE XI  
Atypical (Broncho-) Pneumonias

Type	Serum Treated		Serum and Sulfapyridine		Sulfapyridine		No Serum, No Sulfapyridine		All Cases	
	Number	Died	Number	Died	Number	Died	Number	Died	Number	Died
I	0	—	4 <sup>3</sup>	2 <sup>2</sup>	5 <sup>2</sup>	2 <sup>2</sup>	6 <sup>2</sup>	4 <sup>2</sup>	15 <sup>7</sup>	8 <sup>6</sup>
II	2	1	0	—	1	0	1	0	4	1
III	1	0	5	0	13	3	47 <sup>3</sup>	13 <sup>3</sup>	66 <sup>3</sup>	16 <sup>3</sup>
IV	1	0	0	—	2	0	13 <sup>1</sup>	4 <sup>1</sup>	16 <sup>1</sup>	4 <sup>1</sup>
V	0	—	0	—	1	0	1	1	2	1
VI	1	0	0	—	5	1	23 <sup>1</sup>	6 <sup>1</sup>	29 <sup>1</sup>	7 <sup>1</sup>
VII	2 <sup>1</sup>	1 <sup>1</sup>	1	0	3	0	11	2	17 <sup>1</sup>	3 <sup>1</sup>
VIII	4 <sup>1</sup>	1 <sup>1</sup>	2 <sup>1</sup>	2 <sup>1</sup>	8	2	21 <sup>2</sup>	10 <sup>2</sup>	35 <sup>4</sup>	15 <sup>4</sup>
Others	2 <sup>1</sup>	0	1 <sup>1</sup>	0	21 <sup>1</sup>	8	188 <sup>6</sup>	62 <sup>6</sup>	212 <sup>9</sup>	70 <sup>6</sup>
Total	13 <sup>3</sup>	3 <sup>2</sup>	13 <sup>5</sup>	4 <sup>3</sup>	59 <sup>3</sup>	16 <sup>2</sup>	311 <sup>15</sup>	102 <sup>15</sup>	396 <sup>26</sup>	125 <sup>22</sup>
Per cent died	23		31		27		33		32	
Incidence *	6		10		26		66		38	

Superscripts represent numbers of bacteremic cases.  
\* Per cent of cases that had atypical pneumonia.

Most of the patients with atypical pneumonia received no specific therapy, but among those who were specifically treated, sulfapyridine alone was used in most cases.

The occurrence of antecedent serious illness in the present series of cases is shown in table 12. We have arbitrarily limited the use of the term "secondary" here, as in previous reports, to those cases of pneumonia which occur as terminal events or during acute episodes of serious chronic illness, and to those cases which follow injuries, operations or parturition. Other cases, including those in patients with chronic ailments or alcoholism and those which follow simple respiratory infections, are classed as primary. The incidence of secondary pneumonias among the present cases is shown in table 13. More than one-half of the atypical pneumonias were secondary, as compared with 7 per cent of the cases of lobar pneumonia. Only a small proportion of the cases of secondary pneumonia were given any specific therapy, and most of those received sulfapyridine, either alone or supplemented with serum. The mortality in the secondary pneumonias was high, regardless of the character of the pulmonary lesion. The numbers of cases are too few to judge the relative effects of different kinds of treatment. In

TABLE XII

Serious Antecedent Systemic Complications in Patients with  
Pneumococcic Pneumonia, 1938-39

Antecedent Complication	Serum Treated		Serum and Sulfapyridine		Sulfapyridine		No Serum No Sulfapyridine		All Cases
	Recov- ered	Died	Recov- ered	Died	Recov- ered	Died	Recov- ered	Died	
Chronic pulmonary disease (bronchitis, bronchiectasis, active tuberculosis, asthma)	5 <sup>1</sup>	—	2	1 <sup>1</sup>	13 <sup>2</sup>	2	25	3	51 <sup>4</sup>
Congestive cardiac failure (all kinds)	—	5 <sup>3</sup>	6	5 <sup>4</sup>	6 <sup>1</sup>	6 <sup>2</sup>	13	34 <sup>4</sup>	75 <sup>14</sup>
Coronary thrombosis	—	—	—	1 <sup>1</sup>	—	1 <sup>1</sup>	—	2	4 <sup>2</sup>
Cerebrovascular accidents	—	—	—	—	—	—	5	17	22
Renal failure with or without infection	1	0	3 <sup>1</sup>	3 <sup>3</sup>	1	0	4	13 <sup>4</sup>	25 <sup>8</sup>
Malignant tumors: Lung Others	— 1	— —	— —	1 <sup>1</sup> —	— 1	— —	2 —	5 6 <sup>2</sup>	8 <sup>1</sup> 8 <sup>2</sup>
Pregnancy and/or puerperium	2 <sup>1</sup>	1	3 <sup>1</sup>	—	2	—	1	—	9 <sup>2</sup>
Operations or injuries: Respiratory tract Abdominal Others	3 <sup>1</sup> 4 4	— 1 <sup>1</sup> —	— — —	— — 1 <sup>1</sup>	2 3 <sup>1</sup> 1	— — 3 <sup>1</sup>	4 19 9	2 15 <sup>4</sup> 9 <sup>2</sup>	11 <sup>1</sup> 42 <sup>6</sup> 27 <sup>4</sup>
Cirrhosis of liver, decompensated	—	2 <sup>2</sup>	1	—	—	—	2	2	7 <sup>2</sup>
Severe anemia, blood loss	2	1 <sup>1</sup>	2	—	—	—	1	3 <sup>1</sup>	9 <sup>3</sup>
Diabetic acidosis	1	—	2 <sup>1</sup>	—	1	—	1	2 <sup>2</sup>	7 <sup>3</sup>
Acute poisoning other than alcohol	1	—	—	1 <sup>1</sup>	1	—	—	1	4 <sup>1</sup>
Acute alcoholic intoxication	11 <sup>4</sup>	0	6 <sup>2</sup>	1 <sup>1</sup>	6 <sup>2</sup>	4 <sup>3</sup>	11	6 <sup>2</sup>	45 <sup>14</sup>
Delirium tremens	17 <sup>4</sup>	9 <sup>7</sup>	8 <sup>3</sup>	10 <sup>9</sup>	9 <sup>3</sup>	4 <sup>1</sup>	9	7 <sup>2</sup>	73 <sup>29</sup>

The superscripts represent the numbers of bacteremic cases included.

the specifically treated cases there were 15 deaths among 34 cases with atypical pneumonia (44 per cent) and 12 deaths among 36 with lobar pneumonia (33 per cent). These compare with 50 and 67 per cent deaths among the untreated cases of atypical and lobar pneumonia, respectively.

*Effect of Therapy on the Duration of the Acute Disease.* The frequency with which recovery\* or death occurred at different intervals after the beginning of treatment is shown in table 14. Among the patients who recovered, the average duration of acute symptoms was considerably longer

\* Permanent drop in oral temperature below 100° F. with subsidence of other symptoms of the acute infection.

TABLE XIII  
"Secondary" Pneumonias

Therapy	Atypical (broncho-) Pneumonias		Lobar Pneumonias		Per cent Secondary
	Number	Died	Number	Died	
Specific serum	6 <sup>2</sup>	3 <sup>2</sup>	15 <sup>3</sup>	5 <sup>2</sup>	10
Serum and sulfapyridine	3 <sup>2</sup>	2 <sup>2</sup>	8 <sup>4</sup>	2 <sup>1</sup>	9
Sulfapyridine	25 <sup>2</sup>	10 <sup>2</sup>	13 <sup>6</sup>	5 <sup>3</sup>	17
No serum, no sulfapyridine	174 <sup>12</sup>	87 <sup>12</sup>	18 <sup>3</sup>	12 <sup>3</sup>	41
All cases	208 <sup>18</sup>	102 <sup>18</sup>	54 <sup>16</sup>	24 <sup>9</sup>	25
Per cent died	49		44		
Per cent secondary	53		7		

Superscripts represent numbers of bacteremic cases.

TABLE XIV  
Duration of Symptoms of Acute Pneumonia after the Beginning of Treatment

	No. of Cases	Duration (hours) after Beginning Treatment *							Average Duration† (hours)
		12 or less	12-24	24-36	36-48	48-72	72 or more	Indefinite	
Serum treated	211	97	42	19	10	12	20	11	
Recovered	183	95	40	15	7	8	7	11	21
Bacteremic	38	17	6	6	1	0	1	7	19
Non-bacteremic	145	78	34	9	6	8	6	4	21
Fatal	28	2	2	4	3	4	13	—	145
Bacteremic	21	1	1	4	3	3	9	—	
Non-bacteremic	7	1	1	0	0	1	4	—	
Serum and sulfapyridine	129	33	26	19	10	10	24	7	
Recovered	98	29	24	19	7	8	4	7	23‡
Bacteremic	46	16	10	7	1	4	2	6	23
Non-bacteremic	52	13	14	12	6	4	2	1	23
Fatal	31	4	2	0	3	2	20	—	237
Bacteremic	28	4	2	0	3	2	17	—	
Non-bacteremic	3	0	0	0	0	0	3	—	
Sulfapyridine	225	50	42	50	22	20	33	8	
Recovered	185	37	37	50	18	18	17	8	40
Bacteremic	32	2	8	9	6	2	4	1	50
Non-bacteremic	153	35	29	41	12	16	13	7	38
Fatal	40	13	5	—	4	2	16	—	123
Bacteremic	19	9	4	—	1	—	5	—	
Non-bacteremic	21	4	1	—	3	2	11	—	
No serum, no sulfapyridine	472	77	52	40	31	64	199	9	
Recovered	337	58	39	33	18	45	135	9	96
Bacteremic	3	1	0	0	0	1	1	0	61
Non-bacteremic	334	57	39	33	18	44	134	9	95
Fatal	135	19	13	7	13	19	64	—	158
Bacteremic	27	4	6	1	4	2	10		
Non-bacteremic	108	15	7	6	9	17	54		

\* For the cases receiving neither serum nor sulfapyridine, these refer to the time of admission to the hospital, or the onset of pneumonia when it began in the hospital.

† Cases with indefinite termination are excluded.

‡ These four figures refer to the average number of hours after the first dose of sulfapyridine. The corresponding times after the first dose of serum are 18, 20, 18 and 227 hours, respectively.



when sulfapyridine was used alone than when serum was given, either alone or with the drug. Bacteremic patients responded to treatment with sulfapyridine alone more slowly than non-bacteremic cases, but this was not true among those who received serum, with or without the drug. Fatal cases survived, on the average, much longer following treatment with both agents than after either agent given alone. However, a larger proportion of the fatal cases that were treated with sulfapyridine alone died within 12 or 24 hours after the first dose was given. The long average durations of illness in fatal cases are due to the inclusion of patients who died of purulent or other septic complications.

More than one-half of the patients who were treated with serum alone and recovered without complications had a crisis within 12 hours of the first dose, and 87 per cent were free of acute symptoms within 36 hours.

TABLE XV

A Comparison of the Mortality in Horse Serum Treated Cases and in Those Treated with Rabbit Serums in Pneumococcic Pneumonias of Six Types for Which Both Kinds of Serum Were Available

Type	Patients Treated with Serum (No Sulfapyridine)				Patients Treated with Serum and Sulfapyridine			
	Horse Serums		Rabbit Serums		Horse Serums		Rabbit Serums	
	Number	Died	Number	Died	Number	Died	Number	Died
I	28 <sup>4</sup>	3 <sup>2</sup>	41 <sup>10</sup>	2 <sup>2</sup>	10 <sup>7</sup>	3 <sup>3</sup>	44 <sup>31</sup>	11 <sup>10</sup>
II	5 <sup>1</sup>	1	24 <sup>10</sup>	6 <sup>4</sup>	2 <sup>1</sup>	1 <sup>1</sup>	20 <sup>11</sup>	3 <sup>3</sup>
IV	4	0	7 <sup>2</sup>	0	1	0	2 <sup>2</sup>	1 <sup>1</sup>
V	11 <sup>3</sup>	2 <sup>2</sup>	9 <sup>4</sup>	3 <sup>3</sup>	4 <sup>2</sup>	0	5 <sup>3</sup>	0
VII	13 <sup>1</sup>	1	11 <sup>4</sup>	2 <sup>2</sup>	2 <sup>1</sup>	0	5 <sup>3</sup>	1 <sup>1</sup>
VIII	11 <sup>4</sup>	0	13 <sup>3</sup>	1 <sup>1</sup>	—	—	6 <sup>2</sup>	2 <sup>1</sup>
Age (years)								
Less than 40	48 <sup>3</sup>	2 <sup>1</sup>	63 <sup>17</sup>	4 <sup>3</sup>	10 <sup>5</sup>	1 <sup>1</sup>	29 <sup>16</sup>	7 <sup>7</sup>
40 to 59	21 <sup>4</sup>	3 <sup>2</sup>	33 <sup>12</sup>	8 <sup>7</sup>	5 <sup>3</sup>	1 <sup>1</sup>	29 <sup>17</sup>	5 <sup>4</sup>
60 or more	3 <sup>1</sup>	2 <sup>1</sup>	9 <sup>4</sup>	2 <sup>2</sup>	4 <sup>3</sup>	2 <sup>2</sup>	24 <sup>19</sup>	6 <sup>5</sup>
Day treatment begun								
Third or earlier	26 <sup>3</sup>	1	51 <sup>15</sup>	4 <sup>3</sup>	10 <sup>6</sup>	3 <sup>3</sup>	30 <sup>13</sup>	2 <sup>2</sup>
Fourth	17 <sup>2</sup>	0	15 <sup>4</sup>	1 <sup>1</sup>	3 <sup>1</sup>	0	5 <sup>2</sup>	1 <sup>1</sup>
Fifth	12 <sup>3</sup>	2 <sup>1</sup>	16 <sup>7</sup>	2 <sup>2</sup>	1	0	16 <sup>13</sup>	3 <sup>3</sup>
Sixth	6	1	16 <sup>5</sup>	6 <sup>5</sup>	2 <sup>1</sup>	0	14 <sup>11</sup>	5 <sup>4</sup>
Seventh or later	11 <sup>5</sup>	3 <sup>3</sup>	7 <sup>2</sup>	1 <sup>1</sup>	3 <sup>3</sup>	1 <sup>1</sup>	17 <sup>13</sup>	7 <sup>6</sup>
Total	72 <sup>13</sup>	7 <sup>4</sup>	105 <sup>33</sup>	14 <sup>12</sup>	19 <sup>11</sup>	4 <sup>4</sup>	82 <sup>52</sup>	18 <sup>16</sup>
Per cent died	10		13		21		22	
Per cent bacteremic	18		31		58		63	
Per cent over 40 years	33		40		47		65	

Superscripts represent the numbers of bacteremic cases included

When sulfapyridine alone was used, 41 per cent of the cases reached a similar stage within 24 hours, and 69 per cent within 36 hours, after the first dose. Among the cases treated with both serum and sulfapyridine, 58 per cent had a critical response within 24 hours and 84 per cent had essentially recovered within 36 hours from the time of the first dose of either agent. It is of interest that 40 per cent of the untreated cases that recovered had a crisis within 36 hours of the time of admission to the hospital.

TABLE XVI  
Dosage of Specific Serums

	Serum Alone			Serum and Sulfapyridine		
	Horse	Rabbit	All	Horse	Rabbit	All
Number of patients	73	138	211	19	110	129
Average age (years)	32.6	38.3	36.3	42.1	49.9	48.7
Average dose per patient: Volume (c.c.)	91	47	62	100	59	65
Units ( $\times 1000$ )	159	195	182	202	262	253
Average number of injections per patient	4.0	3.3	3.6	4.5	3.7	3.8
Average time from first to last injection (hours)	17	12	14	19	13	14
Average total dose per patient (Units $\times 1000$ )						
Recovered cases	149	174	165	155	253	246
Fatal cases	251	308	294	380	289	301
Non-bacteremic cases	138	162	152	123	218	204
Bacteremic cases	248	263	259	258	294	289
Average total dose (Units $\times 1000$ ) according to type of pneumococcus						
Type I	175	159	166	200	244	235
II	209	226	257	278	289	288
III	—	221	221	—	244	244
IV	140	189	171	160	250	220
V	174	213	192	145	226	190
VII	151	296	218	270	418	376
VIII	88	140	116	—	255	255
Others	240	190	192	—	267	267
Number of patients receiving different total doses (Units $\times 1000$ )						
Recovered cases						
Less than 50	7	2	9	1	0	1
51-100	15	25	40	4	12	16
101-200	30	62	92	7	28	35
201-400	12	25	37	3	34	37
401 or more	2	3	5	0	9	9
Fatal cases						
Less than 50	0	0	0	0	2	2
51-100	1	1	2	0	2	2
101-200	1	6	7	1	5	6
201-400	4	10	14	1	13	14
401 or more	1	4	5	2	5	7

A comparison of the results of treatment with horse and with rabbit anti-pneumococcus serums is shown in table 15. Only the cases due to the six

common types for which both kinds of serum were available are included in this table. The present data are of interest in view of the recent preliminary report on the use of rabbit serums for Types I, II, V and VII pneumococcus pneumonias at this hospital.<sup>2</sup> The tendency during the present season was to use more of the rabbit serums, particularly in Type II and Type VIII pneumococcal infections. The rabbit serum was used relatively more often in bacteremic cases and in the older patients. In spite of this, the death rates were about the same as among those receiving horse serums, and this was true whether or not sulfapyridine was used in addition.

*Dosage of Serums Used (Table 16).* The average total dose per patient receiving rabbit serum was larger in amount of antibody (units), smaller in volume and was given in fewer injections and over a shorter interval than the average dose of horse serum. This was true, in general, for each of the common types, regardless of whether sulfapyridine was also given. The average potencies of all the serums actually used during this year are given, in units per cubic centimeter, in table 17. The greatest differences in po-

TABLE XVII  
Average Potency \* of Concentrated Antipneumococcal Serums Used during 1938-39

Type	Horse	Rabbit
I.....	2035	4085
II.....	1760	4535
III.....	—	3100
IV.....	3600	4970
V.....	3075	5575
VII.....	4080	9570
VIII.....	1550	4420
Others.....	2000	3880
All.....	2355	4315

\* Expressed in units per c.c.

tency were in the Type II and Type VIII serums, of which the rabbit serums had, on the average, almost three times the concentration of the corresponding horse serums. The average amount of serum used in the patients who also received sulfapyridine was actually greater than in those who received serum alone. The difference in dose, however, was not nearly commensurate with the great difference in the severity of the illness in these two groups of cases, as indicated by the differences in age distribution (table 7) and in the incidence of bacteremia (table 4). An appreciable number of cases recovered after receiving less than 100,000 units and some had a critical response to doses of 50,000 units or less. One-half of the patients who recovered following treatment with serum alone received between 100,000 and 200,000 units. The most frequent dose in the fatal cases was between 200,000 and 400,000 units, even when sulfapyridine was also given. More than two-thirds of those who recovered following treatment with both agents received between 100,000 and 400,000 units of specific antibody.

*Serum Reactions (Table 18).* Immediate reactions, usually considered

TABLE XVIII  
Serum Reactions, 1938-39

	Horse Serums		Rabbit Serums	
	92 Patients	380 Injections	248 Patients	862 Injections
Immediate reactions	29 (32%)	43 (11%)	20 (9%)	26 (3%)
Nausea, vomiting, pains, etc.	12	19	5	6
Urticaria, edema	10	15	4	5
Dyspnea, cyanosis, asthma	4	7	6	9
"Collapse"	7	9	6	10
Chills and febrile reactions	35* (38%)	45* (12%)	112 (45%)	156 (18%)
Severe (106° F. or higher)	3	3	7	7
Delayed serum sickness	23 (25%)		47 (19%)	
Severe symptoms	1		2	

\* Horse serums furnished by the State Laboratory were used for 165 injections in 40 of these patients. Chills followed 38 injections in 29 recipients of these serums.

to be associated with specific sensitiveness, were less frequent in rabbit serum recipients than in those treated with horse serums. Chills were frequent and occurred somewhat more often with the rabbit serums. The great frequency with which chills were encountered is due, in large part, to the fact that almost all of the serums used were furnished for clinical trial. Most of the lots which gave such reactions regularly or which gave rise to severe reactions were not released for general distribution. Severe chills or marked discomfort from serum sickness occurred infrequently.

TABLE XIX  
Dosage of Sulfapyridine Used

	Cases Treated with Sulfapyridine alone					Cases Treated with Sulfapyridine and Serum				
	Recovered	Died	Non-bacteremic	Bacteremic	All Cases	Recovered	Died	Non-bacteremic	Bacteremic	All Cases
Number of cases	185	40	174	51	225	98	31	55	74	129
Average age (years)	44.1	54.1	45.1	48.5	45.8	48.4	49.7	47.5	49.6	48.7
Average total dose (grams)	20.9	18.0	19.5	23.4	20.4	20.1	19.8	13.7	25.3	20.1
Average time from first to last dose (hours)	88	67	80	99	84	81	83	63	95	81
Number of patients who received a total dose of:										
Less than 5 grams	13	12	16	9	25	11	6	9	8	17
6-10 grams	20	10	26	4	30	27	2	19	10	29
11-20 grams	75	7	67	15	82	25	12	15	22	37
21-30 grams	51	5	44	12	56	17	6	7	16	23
31-50 grams	23	2	18	7	25	12	4	4	12	16
51 or more grams	3	4	3	4	7	6	1	1	6	7

*Dosage of Sulfapyridine (Table 19).* In general, each patient received an initial dose of 2 grams. Severe cases received a second dose of 2 grams, two or four hours later. This was followed by 1 gram every four hours. Occasional doses were omitted because of vomiting. The drug was usually given for two or three days after the symptoms of the disease subsided. In some cases the treatment was begun with 1 gram 4-hourly. The average total dose of sulfapyridine used in all cases was about 20 grams given over a period of about 3½ days. It was about the same in those who received serum and in those who were treated with the drug alone. The average dose in bacteremic cases was larger than in non-bacteremic cases and it was given over a longer period. This was particularly true in the patients who received serum in addition.

Among the patients who were treated with sulfapyridine alone and recovered, 18 per cent received 10 grams or less and 68 per cent received between 11 and 20 grams of the drug. Among the 40 fatal cases in this group, 12 (30 per cent) received only 5 grams or less and another 10 (25 per cent) received a total of from 6 to 10 grams of sulfapyridine. Of the patients who were also treated with serum, 41 per cent of those who recovered were given 10 grams or less, and an additional 24 per cent of the cases received between 11 and 20 grams of the drug. Twenty-three of the 31 fatal cases in this group received 11 grams or more of sulfapyridine. Thus only a small proportion of the deaths can be ascribed to inadequate drug therapy, particularly among those who were treated with the combination of serum and sulfapyridine.

TABLE XX

Toxic Effects of Sulfapyridine Among 354 Patients with Pneumococcic Pneumonia Treated with the Drug Alone or in Combination with Serum.

Symptom	No. of Patients
Nausea without vomiting.....	36
Vomiting.....	206
Moderate severity (doses omitted).....	65
Severe (drug discontinued).....	49
Onset after: first dose (1 or 2 grams).....	35
3 grams.....	27
4 grams.....	36
5 grams.....	35
6 to 9 grams.....	45
more than 10 grams.....	28
Stopped, while drug therapy continued, after:	5
less than 12 hours.....	22
1 day.....	21
2 days.....	31
3 or more days.....	31
Anemia (drop of more than 25 per cent in hemoglobin)	7
Acute.....	10
Delayed.....	9
Leukopenia (below 5,000) during treatment.....	16
Renal complication: Hematuria.....	15
Rise in non-protein nitrogen (more than 25 mg. per cent).....	2
Anasarca.....	22
Marked excitement.....	7
Drug fever.....	3
Drug rash.....	34
Fever (above 100° F. by mouth) following cessation of drug therapy...	

*Toxic effects of sulfapyridine* in the present cases (table 20) were similar to those reported from most other clinics. In many instances it was hard to determine whether any given symptom was a manifestation of the pneumonia, or of a complication of the disease, or whether it was due to the drug. Those instances in which there was any serious doubt are excluded from the table.

Vomiting was the most frequent symptom. In 15 per cent of all the cases this symptom was so severe that the drug had to be discontinued. While most of the procedures recommended for the relief of this vomiting were tried, they were only occasionally successful, and then gave only temporary relief. In one-half of the cases the vomiting began within 8 to 12 hours and after only 5 grams or less of the drug had been taken. In 10

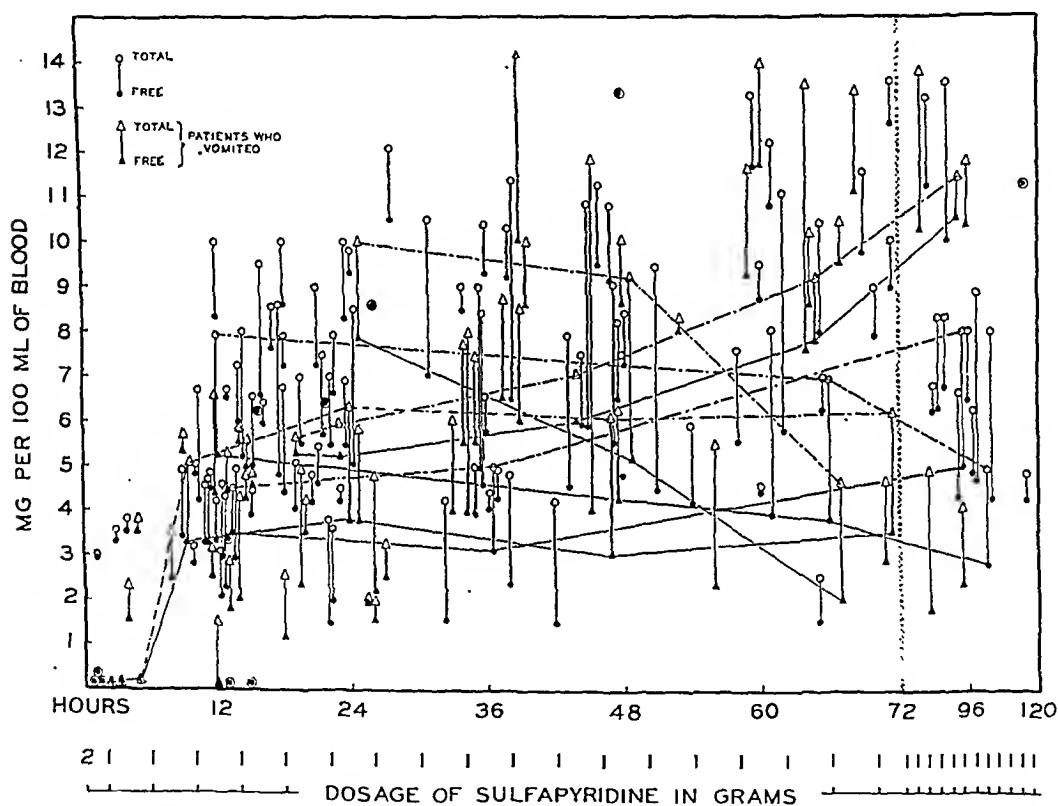


FIG. 1. Blood levels of free and total sulfapyridine in patients who received an initial dose of 2 grams, 1 gram 2 hours later, and then 1 gram every 4 hours. The lines connect determinations made in the same patient at different times.

per cent of the cases the vomiting began soon after the first dose. In some of the cases the drug was given without interruption in spite of the nausea and vomiting, which later subsided after varying intervals while the drug was still being taken. The vomitus in a few cases contained considerable amounts of fresh blood. The acute anemias and leukopenias usually occurred between the second and fifth day. Hemoglobinuria and jaundice did not occur in these cases, nor was agranulocytosis encountered. These reac-

tions were observed in patients who were treated with sulfapyridine during this season for infections other than the pneumococcic pneumonias. Anemias that occurred late in the patients who had purulent complications are not included. This would account for the low incidence of this reaction, since in most of the uncomplicated cases the drug was discontinued within from three to six days. Leukopenias are included here only if they occurred in patients who had leukocytosis before the drug was given. This complication was noted within two or three days after treatment began and thus differs from the agranulocytosis noted in other cases, both in this hospital and elsewhere. On the whole, except for vomiting and occasional severe renal symptoms, the reactions to the drug in the cases of pneumococcic pneumonia were not frequent. This may be due, in part, to the fact that the average duration of treatment was relatively short (table 19) and perhaps, in part, to the close supervision of the cases throughout treatment.

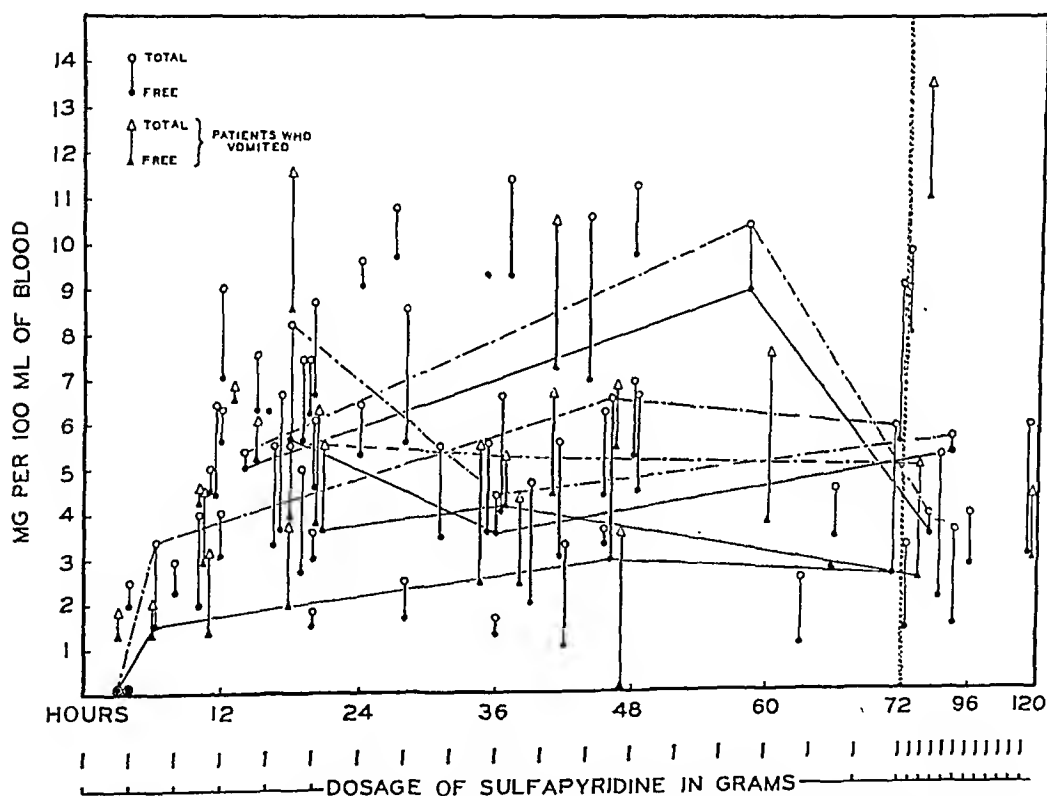


FIG. 2. Blood levels of free and total sulfapyridine in patients who received 1 gram every 4 hours. The lines connect determinations made in the same patient.

Blood concentrations of sulfapyridine<sup>4</sup> varied considerably in different patients even on the same dosage. Although the fluid exchange was not measured accurately, there did not seem to be any regular and close correlation between fluid intake and the concentration of the drug in the blood. The levels attained and the degree of acetylation did not seem to be related to the amount of vomiting. These findings are shown graphically in figures 1 and 2.

TABLE XXI  
Postpneumonic Complications

Complication	Serum Treated		Serum and Sulfapyridine		Sulfapyridine		No Serum No Sulfapyridine		All Cases
	Recov- ered	Died	Recov- ered	Died	Recov- ered	Died	Recov- ered	Died	
Empyema *	7 <sup>4</sup>	2 <sup>1</sup>	7 <sup>7</sup>	5 <sup>5</sup>	7 <sup>1</sup>	2 <sup>2</sup>	4	3	37 <sup>20</sup>
Sterile pleural effusion	4	—	6 <sup>2</sup>	—	6 <sup>1</sup>	—	4	—	20 <sup>3</sup>
Pericarditis	1	2 <sup>1</sup>	1 <sup>1</sup>	3 <sup>3</sup>	—	1 <sup>1</sup>	—	1	9 <sup>6</sup>
Endocarditis	—	5 <sup>4</sup>	—	4 <sup>4</sup>	—	1 <sup>1</sup>	—	1 <sup>1</sup>	11 <sup>10</sup>
Pulmonary abscess	1 <sup>1</sup>	—	—	3 <sup>2</sup>	1	—	1	3	9 <sup>3</sup>
Meningitis	—	1 <sup>1</sup>	—	1 <sup>1</sup>	—	2 <sup>2</sup>	—	2 <sup>2</sup>	6 <sup>6</sup>
Arthritis	—	1 <sup>1</sup>	1 <sup>1</sup>	1 <sup>1</sup>	—	—	—	1	4 <sup>3</sup>
Peritonitis	2 <sup>2</sup>	—	1 <sup>1</sup>	—	—	—	—	—	3 <sup>3</sup>
Thrombophlebitis	1	1 <sup>1</sup>	2 <sup>2</sup>	1 <sup>1</sup>	2 <sup>1</sup>	1	1	1	10 <sup>5</sup>
Otitis media	3	—	2 <sup>2</sup>	—	2 <sup>1</sup>	—	9	1	17 <sup>3</sup>
Streptococcic infection	1 <sup>1</sup>	4 <sup>3</sup>	2 <sup>2</sup>	2 <sup>1</sup>	1	1 <sup>1</sup>	4	5	20 <sup>8</sup>
Subcutaneous abscess	3 <sup>1</sup>	—	2	—	1	1 <sup>1</sup>	—	2	9 <sup>2</sup>
Atelectasis	4 <sup>3</sup>	—	3	—	2 <sup>1</sup>	—	1	2	12 <sup>4</sup>
Relapse	1	2 <sup>2</sup>	1 <sup>1</sup>	—	1 <sup>1</sup>	3 <sup>1</sup>	4 <sup>1</sup>	—	12 <sup>6</sup>
Jaundice before treatment	6 <sup>1</sup>	1 <sup>1</sup>	8 <sup>4</sup>	—	8 <sup>1</sup>	2 <sup>2</sup>	2	3 <sup>1</sup>	30 <sup>10</sup>
Leukopenia (4,000 or less) before treatment	1	2 <sup>2</sup>	2 <sup>2</sup>	—	—	—	1	—	6 <sup>4</sup>

The superscripts represent the numbers of patients in whom pneumococci were cultured from the blood.

\* Among the patients with empyema only 1 in each group recovered without operative intervention other than thoracentesis.

*Post-Pneumonic Complications (Table 21).* Purulent complications and endocarditis were relatively more frequent in the patients treated with both serum and sulfapyridine than among the other cases. This was to be expected from the high incidence of bacteremia.<sup>5</sup> Patients who were admitted for post-pneumonic complications and whose pneumonia was not active at the time are not included in this series of cases. Empyema was the most frequent purulent complication. It is of interest that in the absence of bacteremia it occurred most often in those patients who received either no specific therapy or only sulfapyridine. In the sulfapyridine treated patients who developed septic complications, treatment with the drug in full doses was usually continued for several days in an attempt to eliminate the focus of infection without surgical intervention. As noted in the table, this was not successful, at least in the cases with empyema. In the patients with pericarditis who recovered, this complication was diagnosed on the basis of a definite pericardial friction rub and was considered to be a fibrinous pericarditis without extensive effusion. In those who died, purulent fluid was found in the pericardial cavity. The relatively frequent occurrence of pneumococcic endocarditis in the present series of cases is perhaps dependent on the fact that a considerable number of severely infected patients were kept alive for a longer time than usual with the therapy employed. Hemolytic streptococcus infections occurring during the course of recovery



from the pneumococcic pneumonias were quite frequent. Their occurrence during sulfapyridine treatment or, in some cases, shortly after the drug was discontinued, is of some interest. A number of these patients had blood stream invasion with this organism (table 5). A number of patients with jaundice complicating the pneumonia were treated with sulfapyridine without ill effects. In these cases the drug was discontinued soon after the fever and symptoms subsided.

Of special interest are the cases in which there was a relapse, that is, a recurrence of acute pneumococcic pulmonary infection within a few days and during the patient's stay in the hospital. Only brief mention of the treated cases need be made here. Of the three serum treated cases, two had Type I pneumonia without bacteremia and apparently responded well to treatment. One of these patients later had Type XIX pneumococcic pneumonia with a negative blood culture and recovered without treatment, the other developed a Type V infection with bacteremia and died in spite of specific serum treatment. The third patient was treated with serum for Type VII pneumonia and recovered completely but remained in the hospital under observation for hyperthyroidism. Two months later he developed Type I pneumococcic pneumonia with bacteremia and died in spite of serum treatment. The patient with relapse listed as treated with serum and sulfapyridine received this therapy for a Type I pneumonia with bacteremia which occurred after apparent recovery from a Type III pneumococcus pneumonia without bacteremia which was treated with sulfapyridine alone. The four patients who were treated with sulfapyridine alone had the same type of pneumococcus during the relapse as in the original infection. All were treated with the drug during both episodes. None had bacteremia during the relapse. One had Type I, two had Type III and one had Type VIII pneumococcic pneumonia. One of the Type III cases that had bacteremia when first admitted is included here although he was discharged from the hospital before his reinfection.

*Sulfanilamide* was used in full doses either alone or as a supplement to specific serum treatment in 138 cases of whom 32 (22 per cent) died. The cases are listed in table 22. Most of the patients treated with this drug alone were due to either Type III or to "higher" types of pneumococci. A large proportion of them (47 per cent) were atypical and only 14 per cent had positive blood cultures. The serum treated patients to whom this drug was given all had typical lobar pneumonia and more than one-half of them had positive blood cultures. The effect of the sulfanilamide on the death rate is difficult to evaluate but it certainly was not very striking.

It is of interest that 10 of the sulfanilamide treated cases developed anemia of a moderate degree (that is, a drop in hemoglobin of more than 25 per cent). This was associated with hemoglobinuria and jaundice in one case. One patient with Type V pneumonia and bacteremia who was treated with sulfanilamide alone developed an extensive drug rash and jaundice

TABLE XXII

Cases of Pneumococcic Pneumonia to Whom Sulfanilamide Was Given in Full Doses Either as the Only Specific Therapy or as a Supplement to Specific Serum 1938-39

Pneumococcus Type	Sulfanilamide Used Alone *		Serum and Sulfanilamide †	
	Recovered	Died	Recovered	Died
I	1	0	9 <sup>2</sup>	2 <sup>2</sup>
II	2 <sup>1</sup>	0	5 <sup>4</sup>	4 <sup>3</sup>
III	12	4	5 <sup>1</sup>	1 <sup>1</sup>
IV	2	1	—	—
V	2 <sup>1</sup>	2 <sup>1</sup>	5 <sup>2</sup>	2 <sup>2</sup>
VI	4	2	1	0
VII	2	0	3 <sup>1</sup>	1 <sup>1</sup>
VIII	4 <sup>1</sup>	1 <sup>1</sup>	1 <sup>1</sup>	1 <sup>1</sup>
Others	43 <sup>4</sup>	10 <sup>4</sup>	5 <sup>3</sup>	1
Total	72 <sup>7</sup>	20 <sup>6</sup>	34 <sup>14</sup>	12 <sup>10</sup>
All "atypical" (broncho) pneumonias	34	9	—	—

Cases to whom sulfapyridine was also given are excluded.

Superscripts represent the numbers of bacteremic cases included.

\* These cases are listed in all other tables as untreated, i.e., under "no serum, no sulfapyridine."

† These cases are listed in other tables as treated with serum alone.

associated with hepatomegaly. The death of this patient may have resulted from the toxic effects of the drug, since all the blood cultures taken after treatment were sterile and specific antibodies had developed in the blood.

#### COMMENT

We have been concerned in this paper with a presentation of the results of therapy and an analysis of the important factors influencing these results. It should be apparent from this study that it is difficult, if not sometimes impossible, to interpret the results obtained in many other clinics when adequate data are not presented and particularly when previous experience with similar cases is not available for comparison. It is natural that a remedy like sulfapyridine, which has a wide application, is inexpensive and involves little effort on the part of the physician would be used much more extensively than an agent like specific serum, which involves considerable conscientious effort, intelligence and experience. No attempt will be made to compare the present cases with those published from other clinics.

The data presented are purposely limited to the pneumococcic pneumonias in adults, since such cases have been studied most extensively in the past and also because they present a more nearly uniform group of infections. To be sure, in many of the cases associated with the so-called higher types of pneumococci, the etiological relationship of the organisms to the disease is not always definite, nor are the clinical pictures presented always

very typical. Both the good and the poor results in many such cases are open to criticism, particularly when no corroborating bacteriological findings from blood, lung or exudates are available. The comparison between serum and chemotherapy in such cases is most unsatisfactory.

It is apparent that both serum and sulfapyridine were highly successful in curtailing the death rate and in bringing about a rapid termination of the symptoms of acute infection. Failures with both kinds of therapy still occur. They are most frequent in aged individuals, in patients treated late in the disease and in those with preëxisting systemic diseases. Delayed deaths also occur from complications of the pneumonia, which are frequently present at the time treatment is instituted and which are not adequately influenced by the treatment.

A number of important factors have not been considered in the present analysis. These include many bacteriological details, particularly the incidence of mixed infection, the effect of persistent vomiting on the results of sulfapyridine therapy and the differences in response to sulfapyridine between cases treated early and those treated late in the disease. Adequate data for the proper interpretation of the significance of some of these factors are lacking. The antibody response in patients treated with sulfapyridine and its possible significance are considered elsewhere.<sup>6</sup> We have also reported separately on the intravenous use of the sodium salt of sulfapyridine in some of the present cases.<sup>7</sup>

### SUMMARY AND CONCLUSIONS

The significant factors concerning the results of treatment in 1037 cases of pneumococcic pneumonia admitted to the Boston City Hospital during the 1938 to 1939 season have been analyzed. Specific serums and sulfapyridine were each found to be effective in reducing the death rate and in bringing about rapid clinical improvement. The combination of serum and sulfapyridine was effective in the cases with the worst prognosis.

Both horse and rabbit serums were effective, but the latter were more concentrated and were used in the poorer risks. Rabbit serums gave fewer allergic reactions than horse serums. Severe untoward reactions from either serum or sulfapyridine were infrequent.

Sulfanilamide was not very effective either when given alone or as a supplement to serum therapy.

On the basis of the results in these cases it is felt that the optimum treatment for the pneumococcic pneumonias should be carried out, in general, as follows: (1) Blood culture and sputum typing should be done as soon as the clinical diagnosis of pneumonia is made. (2) Sulfapyridine therapy should be started at this time. (3) Specific serums should be given to the cases with the worst prognosis as soon as the type is determined. (4) Serum should be given in all cases when there is no definite improvement after 24 to 36 hours of sulfapyridine therapy.

The authors are grateful to the visiting physicians and resident staffs of the various Medical Services and of the Mallory Institute of Pathology for their generous coöperation. They are also indebted to Mildred W. Barnes and Claire Wilcox for technical assistance, to Kathleen Daley and Winifred Doyle for the pneumococcus typing and to Margaret A. Adams and Nancy E. Marean for the chemical determinations.

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# RELATIONS BETWEEN AGE AND WEIGHT AND DOSAGE OF DRUGS \*

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BECAUSE of the existence of individual variability in response to drugs, no method can be devised for determining accurately in advance the proper dosages of drugs for individuals. Average doses, suitable for large groups of adult patients, have been worked out empirically and are printed in pharmacopoeias. This paper is concerned with a survey of methods by which drug dosage might be modified for age and size of individual.

It is natural to proportion dosage according to size of patient, and I suppose it was done even by our Stone Age ancestors. We have today a rule for doing this, Clark's rule, or the weight rule, to take the adult dose as that for a person weighing 150 lbs. and change the dose as necessary in direct proportion to the weight of the patient. The weight rule is represented in figures 1, 2 and 3 by the diagonal straight lines. A person of weight 70 kg. (154 lbs.) is to receive 100 per cent of the adult dose; percentages for those of lesser weights may be read off directly from figures 1, 2 and 3, and for those of greater weights from figure 3, line 1.0.

It is not always possible to ascertain a patient's weight. A number of rules have, therefore, been worked out for estimating the dose from the age in such ways that the computed dose would be very close to that called for by weight. J. Young<sup>21</sup> in 1813 stated that "for children under 12 years old, the doses of most medicines must be diminished in the proportion of the age to the age increased by twelve: for example, at two years old  $\frac{1}{7} = 2/(2 + 12)$ . At 21 the full dose may be given."

In order to facilitate comparison of the results of using different possible methods of computing dosage, the ages of boys up to 17 years have been set on the bottom line of figure 1 with graduations corresponding to the average weights of boys at different ages, taken from the tables of Davison<sup>28</sup> (for 14 years and under) and Emerson and Manny<sup>30</sup>; the underlying data are shown in table 1. Figure 2 is a corresponding chart for girls. The small drop in weight during the first week of life is disregarded. With this age scale to plot the results of using Young's rule, we find that there is a rough approximation to the average weight rule figures from two years of age up to about the onset of puberty. Bastedo's rule,<sup>4</sup> using the multiplier (age in years plus 3)/30 gives a really beautiful approximation, starting at 1 year, to the average weight rule for children (see figures 1 and 2) and is well worth remembering. The rules of Cowling (age next birthday/24) and Dilling<sup>23</sup> (age/20) are not so good as Bastedo's; they have been omitted

\* Read at the New Orleans meeting of the American College of Physicians, March 31, 1939.

† Deceased September 19, 1939.

from figures 1 and 2 to avoid the confusion that would result from plotting five interlacing lines.

Fried's rule,<sup>34</sup> for infants below one year, gives comparatively small doses. Fried introduced the multiplier, age in months/150, and pointed

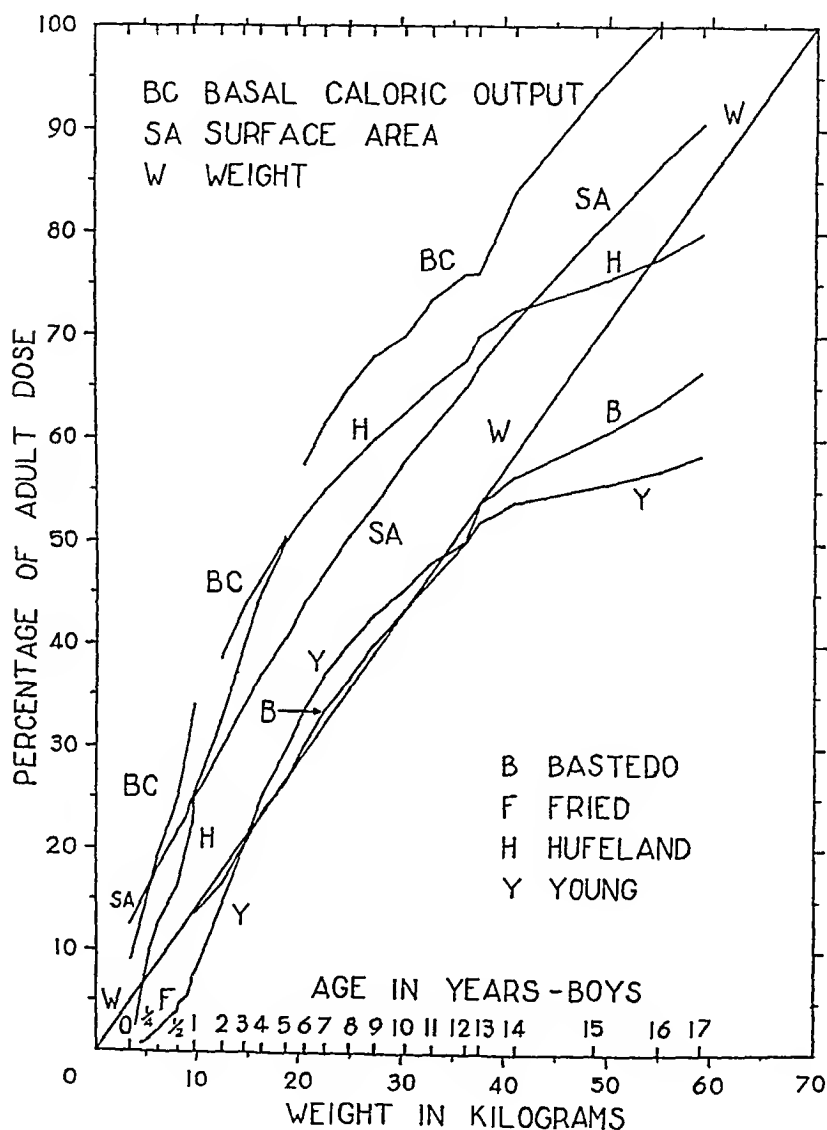


FIG. 1. Possible bases for proportioning dosage to child age or weight: basal caloric output per 24 hours, surface area, weight with 70 kg. as "adult" weight; Hufeland's method (see text); adult dose multiplied by age in months/150 (Fried, for infants under one year); age in years/age in years plus 12 (Young, for ages below 12 years); (age in years plus 3)/30 (Bastedo).

out that he was thus practically extending Young's rule into the first months of life, since the exact multiplier would be: age in months/(age in months plus 144). All the age rules, except Bastedo's,<sup>4</sup> give doses for the first year of life that are usually below those given by the weight rule. This brings

us to an important point in relation to dosage. It has been and is felt very strongly by many physicians that great caution must be used with regard to dosage for patients at both extremes of life, infancy and old age, and that one should not disregard the obvious truth that a dose too small can be increased, but a dose too large may be irremediable.

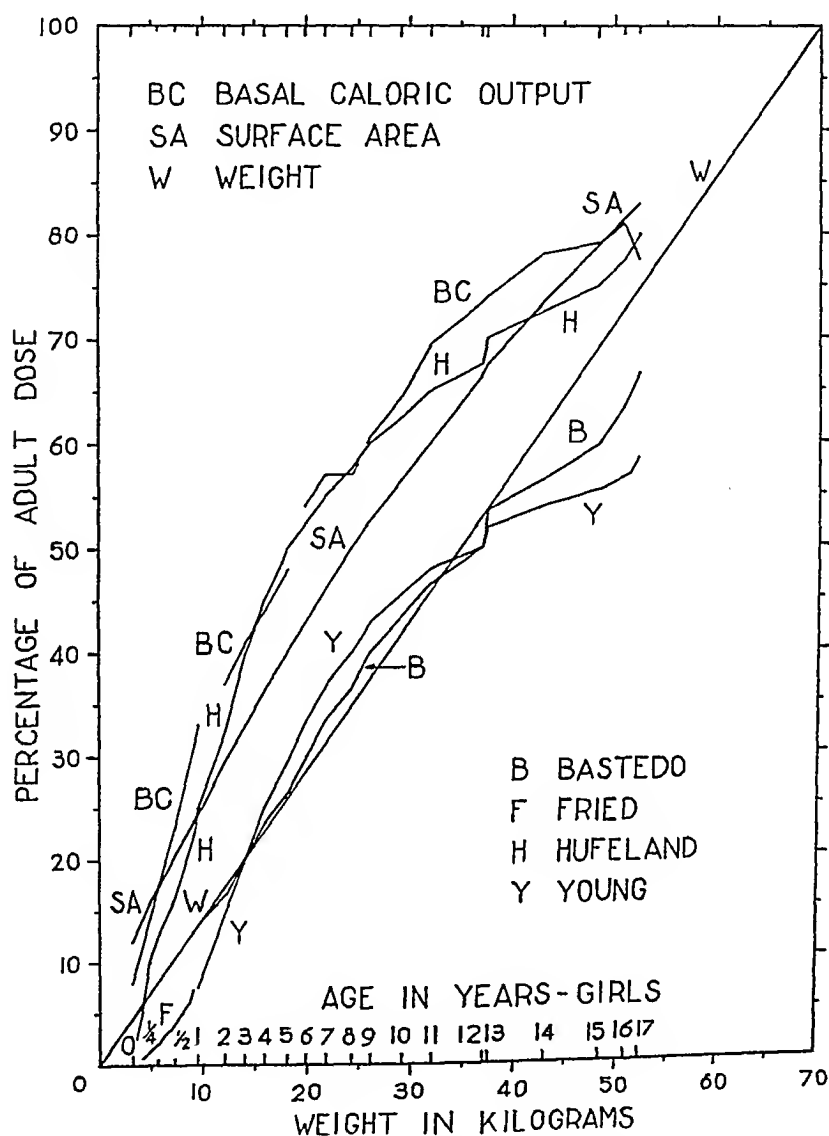


FIG. 2. Possible bases for proportioning dosage to child age or weight: basal caloric output per 24 hours, surface area, weight with 70 kg. as "adult" weight; Hufeland's method (see text); adult dose multiplied by age in months/150 (Fried, for infants under one year); age in years/age in years plus 12 (Young, for ages below 12 years); (age in years plus 3)/30 (Bastedo).

On the other hand there have been, and are today, many physicians of great experience, who, while admitting the force of the argument for caution, incline to the view that infants and children are in proportion to their weight

more tolerant of many drugs than are adults, except possibly during the early days or weeks of life. An expression of this view is shown in figures 1 and 2 in the line drawn from Hufeland's method. Hufeland<sup>31, 41</sup> took as adult dose the figure 40, to be given at age 25. At one-half month of age the dose was to be 1, at one month 2, at two months 4, at three months 5; then increasing every two months by 1, becoming at 11 months 9, at one year 10, at three years 16, at five years 20, at 15 years 30, at 20 years 35; the initial doses always somewhat less, until individual sensitivity had been determined. These figures have been obtained through the kindness of Professor George B. Roth.

TABLE I  
Heights, Weights, Surface Areas and 24-Hour Basal Caloric Requirements  
of Males and Females

Age	Height (nearest cm.)		Weight kg.		Surface Area in Square Meters				Basal Caloric Requirement 24 hours	
					DuBois		DuBois- Pfaundler			
	M	F	M	F	M	F	M	F	M	F
Birth	52	52	3.4	3.2	.21	.21	.23	.22	159	145
1 month	54	53	4.4	4.1	.24	.23	.26	.25	—	—
2 months	57	56	5.3	4.8	.27	.26	.30	.28	—	—
3 months	60	59	6.1	5.7	.30	.29	.33	.31	332	307
6 months	67	66	8.1	7.3	.37	.35	.40	.37	442	401
8 months	70	68	8.9	8.2	.40	.37	.42	.40	—	—
12 months	75	73	9.7	9.5	.43	.42	.46	.45	595	584
2 years	85	85	12.4	12.1	.52	.52	.55	.54	— (680)	— (650)
3 years	94	92	14.6	14.0	.60	.58	.62	.60	— (770)	— (720)
4 years	99	99	16.3	15.9	.66	.65	.67	.67	— (820)	— (780)
5 years	106	105	18.7	18.1	.73	.72	.74	.73	— (890)	— (840)
6 years	112	111	20.5	19.9	.79	.78	.80	.79	1010 (940)	950 (880)
7 years	118	116	22.5	21.8	.86	.83	.86	.84	1080 (990)	1000 (910)
8 years	123	122	24.8	24.3	.92	.91	.92	.91	1140 (1040)	1000 (960)
9 years	127	126	27.3	26.1	.98	.96	.98	.96	1200 (1080)	1060 (990)
10 years	133	131	30.3	29.2	1.06	1.03	1.06	1.03	1230 (1135)	1140 (1030)
11 years	137	136	32.9	32.0	1.12	1.10	1.12	1.10	1290 (1170)	1220 (1060)
12 years	142	144	36.2	37.0	1.20	1.22	1.19	1.21	1350 (1220)	1290 (1140)
13 years	145	146	37.5	37.5	1.24	1.24	1.23	1.23	1350 (1220)	1300 (1110)
14 years	151	153	41.0	43.0	1.32	1.36	1.31	1.35	1480	1370
15 years	160	156	48.7	48.4	1.48	1.45	1.47	1.44	1640	1390
16 years	165	158	54.9	50.9	1.60	1.50	1.58	1.49	1770	1420
17 years	169	159	59.0	52.3	1.68	1.52	1.66	1.52	1800	1360
Adult	173	—	70.0	—	1.83	—	1.83	—	1760	—

N.B. Height and weight values of children from Davison<sup>18</sup> (12 years and under) and Emerson and Manny.<sup>30</sup> Surface area values, "DuBois," calculated from DuBois formula; "DuBois-Pfaundler" calculated from new formula (see text). Basal caloric requirement—values for 12 months and under calculated from data of Talbot, Wilson and Worcester<sup>66</sup> (obtained from females); bracketed values from Lewis, Kinsman and Iliff<sup>47</sup>; remaining values from Boothby, Berkson and Dunn.<sup>10</sup>

Those physicians who believe in the greater proportionate tolerance of the young for drugs have in recent years received support from some laboratory workers. In 1909 the biochemist Benjamin Moore<sup>53</sup> advocated giving doses of drugs in proportion to the  $\frac{2}{3}$  power of the body weight, or  $W^{.67}$ , because it approximates a surface area rule. Giving drugs in direct propor-



tion to body weight is in terms of exponents, or powers, to follow the rule  $W^{1.0}$ . If we use a power less than 1.0, we give the young of a species proportionately larger doses than adult members of the species, and the smaller the power the bigger the proportion of the adult dose that the young receive. This is illustrated by figure 3, in which the doses given by various powers

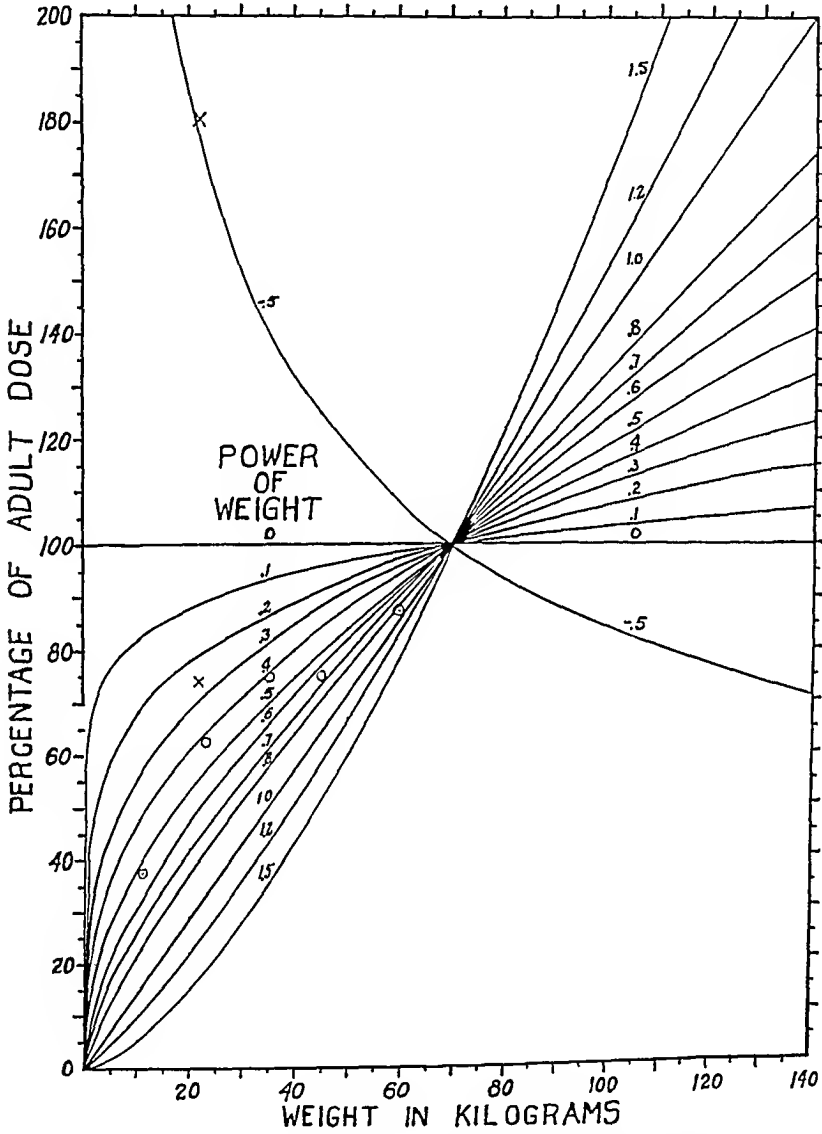


FIG. 3. Percentage of adult dosage that would be given if dosage were proportioned to various powers of the body weight, giving 100 per cent of adult dose to patients of 70 kg. Line 1.0 is that of direct proportion to weight,  $W^{1.0}$ . Upper x percentage of adult maintenance dose of digitalis for a group of children averaging 22 kg.,<sup>42</sup> possibly maintenance dosage would follow line  $-.5$ . Lower x percentage of adult digitalizing dose for same group of children; possibly digitalizing dose would follow line .3. Circles show percentages of dose of sulfanilamide for 70 kg. patient used by Long, Bliss and Feinstone<sup>50</sup> to attempt quickly to initiate blood levels of 10 to 15 mg. per 100 c.c.; appear to average on line .5 (cf. figure 5). Curves calculated from the relation,  $\log \text{dose} = 2 + P (\log \text{weight} - \log 70)$ . P = power.

of the weight are shown. If we use the zero power of the weight, or  $W^0$ , we give all patients 100 per cent of adult dose, regardless of weight. The rule for  $\frac{2}{3}$  power of the weight, or  $W^{.67}$ , is not shown, but  $W^{.7}$  gives a good approximation and also illustrates very nearly the effect of using  $W^{.67}$  or  $W^{.72}$ , a rule advocated by Dreyer and Walker,<sup>25, 26</sup> because of the approximation to a surface area rule. Bazett and Quinby<sup>5</sup> found a satisfactory adjustment by this rule of the anesthetic dose of urethane in the cat. There is evidence, however, that for certain drugs at least, simple mathematical relations of any type based on weight are not likely to hold at the extremes of life (see figure 4, and barbiturates, below).

Returning to figures 1 and 2 we find a surface area rule plotted. This rule follows rather closely the line for a rule on the basis of the  $\frac{2}{3}$  power of the body weight, or  $W^{.67}$ . The values underlying the surface area lines in figures 1 and 2 have been plotted from a new formula, calculated without arbitrary restrictions by the standard mathematical method of multiple regression. It is of interest to note that this method was originally devised by one of the greatest of mathematicians, Gauss,<sup>7</sup> and published in 1821–1826.<sup>64</sup> The DuBois<sup>27</sup> formula:  $\log SA = .725 \log H + .425 \log W + 1.8564$  or any other derived from the same nine subjects cannot be used for infants without some commission of the mathematical sin of extrapolation, since the smallest subject weighed 6.27 kg. The data have, therefore, been extended by addition of figures on 12 infants measured by Pfaundler<sup>56</sup> in Germany, by a method very similar, after it was found that multiple regressions computed (Fisher,<sup>33</sup> sect. 29) from the logs<sub>10</sub> of the two sets did not differ significantly (P. 9, Fisher,<sup>33</sup> sect. 26); this implies that the technic used in the two sets of measurements of the body surface was substantially the same. Pfaundler's 12 infants weighed 2.00 to 5.80 kg. The new formula computed (Fisher,<sup>33</sup> sect. 29) for the whole 21 subjects is:

$$\log SA (\pm .004) = .456 (\pm .084) \log H + .509 (\pm .032) \log W + 2.302.$$

This is not by any means a final surface area formula; but proper statistical investigation for homogeneity of the rather numerous groups of surface area measurements in the literature (see Boyd<sup>11</sup>) would be very laborious, and probably without any great improvement resulting. The surface areas computed by the two formulas are given in table 1. The DuBois formula<sup>27</sup> underestimated the surface area of 10 of Pfaundler's 12 infants, the new formula five of 12 with one other almost exact; both formulas underestimated in five of the nine DuBois subjects. Both give 1.83 square meters for the surface area of an adult of height 173 cm. and weight 70 kg., which have been taken as "average male adult" (really about 30 years of age) figures for the purpose of computing values for the surface area lines. Table 1 shows little divergence between results of use of the two formulas except for infants.

Figures 1 and 2 also show lines for proportioning dosage to 24-hour basal caloric requirement, taking 1760 as the normal adult figure. There are

three lines shown. The top line, for six years and up, from the data of Boothby, Berkson and Dunn,<sup>10</sup> is based on results on normal subjects at the first basal metabolic rate reading. The middle line, from two to five years, is based on the extensive material of Lewis, Kinsman and Iliff,<sup>47</sup> on subjects who were studied on different occasions during the growth period. Below two years the figures are calculated from those of Talbot, Wilson and Worcester,<sup>66</sup> for girls, which are probably not particularly different from those for boys at this early age. It will be noted that dosage on this basis would increase very abruptly with age, from about 9 per cent of adult dose at birth to 25 per cent at six months, 50 per cent at about five years and 75 per cent at 11 years (boys, girls 13).

The possible importance of basal caloric output in connection with drug dosage has been pointed out particularly for morphine.<sup>37</sup> Morphine is generally considered poorly tolerated in infants and old people. In old age and during the first few weeks after birth dosage on the basis of basal caloric output would be lower than at intermediate ages, but on this basis would become relatively high at six to 12 months of age (figures 1 and 2), so that the danger from morphine is probably connected with some other factor than basal caloric output, possibly with a high sensitiveness of the respiratory center. Use in the mother late in labor, within less than about four hours prior to delivery, is likely to cause respiratory depression in the child delivered.<sup>60</sup> Bastedo<sup>4</sup> states that he has seen a child of one year "doped" by gr.  $\frac{1}{20}$  of powdered opium, or only about gr.  $\frac{1}{200}$  (0.3 mg.) morphine, or about gr.  $\frac{1}{160}$  morphine sulfate. Schlossmann<sup>57</sup> says, "in infants symptoms which threaten life may appear after one drop of opium tincture" and recommends that neither morphine nor any preparation containing opium be given before the fourth year of life "without the most urgent indications." An important practical point to emphasize here is the great natural individual variability in response to drugs. Serious respiratory depression, or actual apnea, may occur in an occasional patient of any age even from what had been thought a very safe dose of morphine. Caution is necessary in giving morphine to any patient whose susceptibility to morphine has not been determined, and especially so in the young and the aged. Though it is not the controlling factor, basal metabolic rate is of some importance. Ordinary morphine dosages are considered dangerous in markedly hypothyroid patients. Guedel<sup>37</sup> states that a patient in postoperative thyrotoxin storm will destroy gr.  $\frac{1}{4}$  (16 mg.) morphine sulfate in one or two hours, while in the aged gr.  $\frac{1}{6}$  (11 mg.) will still be effective after six or eight hours. In some old people gr.  $\frac{1}{8}$  (8 mg.) may be a dangerous dose of morphine sulfate. Thus, it seems that, taking as standard the official U. S. P. dose of 8 mg. (gr.  $\frac{1}{8}$ ) and regulating the dosage of morphine for infants, children or the aged, in direct proportion to weight, may result in giving a dangerous dose.

Codeine phosphate is given by Pfaundler and Schlossmann<sup>57</sup> in infants

4 to 12 months of age in doses of 1 to 5 mg. Their extensive table of drug dosage for infants and children merits study.

The dosage of antiluetic drugs is commonly made larger for children than for adults in proportion to weight. Thus, children may be given 15 mg. neoarsphenamine per kg. after the preliminary small initial doses,<sup>18</sup> while the corresponding doses for adults are only about 9 mg. per kg. (dose of 0.6 gm.). Even greater differences are made in one large clinic<sup>13</sup> as shown in table 2 for "old arsphenamine," bismuth, and mercury salicylate, infants

TABLE II  
Dosages of Antiluetic Drugs, Vanderbilt Clinic, New York<sup>13</sup>

Drug	Alternate Plan		Infants and Children			
	Men	Women	Birth to 6 months	6 months to 1 year	1 year to 6 years	6 to 14 years
Old Arsphenamine						
Initial dose	0.2	0.15	0.075	0.1	0.1	0.15
Fourth week	0.3	0.2	0.1	0.15	0.15	0.2
1st course						
Seventh week						
1st course	0.4	0.35	0.1	0.15	0.2	0.25
2nd course	0.5	0.4				
Mercury Salicylate						
Initial	gr. 3/4		gr. 1/10	gr. 1/4	gr. 1/4	gr. 1/4
Maximum	gr. 1-1/2		gr. 1/2	gr. 1/2	gr. 1/2	gr. 1
Bismuth *						
Initial	1 c.c.		1/4 c.c.	1/2 c.c.	1/2 c.c.	1 c.c.
Maximum	2 c.c.		1 c.c.	1 c.c.	1 c.c.	1-1/2 c.c.

\* Based on preparations containing 50 mg. of elemental bismuth per c.c.

receiving 20 per cent of the maximum adult dose of old arsphenamine, 33 per cent of that of mercury salicylate, and 50 per cent of that of bismuth. It is interesting to compare these with the dosages indicated by various rules in figures 1 and 2. Because of the step-like increases of antiluetic dose with increasing age, it is difficult to formulate the rate of increase.

A number of other drugs seem to be tolerated better by children than would be expected from the results of applying any of the commonly used dosage rules. Thus, Bastedo<sup>4</sup> states that "the child's dose of a cathartic or belladonna or arsenic approaches that of an adult." He cites two interesting paired observations in human pharmacology: (1) "we have seen the same amount of belladonna given to a father and to his son six years of age with equal effect," and (2) "a child of three not one whit more affected by a grain of calomel than was her mother by half the dose." Pfaundler and Schlossmann<sup>57</sup> show the dose of castor oil for infants 4 to 12 months of age as 5 to 10 c.c.; the British Pharmacopoeia (1932) gives the adult dose range as 4 to 16 c.c.

Atropine is sometimes administered practically to the limit of tolerance to

infants in pyloric stenosis and to adults in postencephalitic Parkinsonism. Assuming complete absorption, which is here rather unlikely, infants of two to four weeks, averaging about 3.9 kg., may possibly tolerate total daily dosage of about 1.5 mg.,<sup>60</sup> 16 to 20 per cent of the corresponding adult figure, also producing symptoms of beginning atropine poisoning, which is 7 to 9 mg.<sup>86</sup> Infants thus may possibly tolerate two or three times as much atropine as would be expected on the basis of weight.

In pharmacological experiments it is common, despite the warnings of Moore,<sup>53</sup> Dreyer and Walker,<sup>25</sup> Bazett and Erb,<sup>6</sup> and others, to proportion dosage of drugs to the weight of the animal, assuming that unusual results, at least within the same species, are accountable for on the basis of individual variation. My satisfaction with this procedure was finally upset by the results shown in table 3, obtained by titration of morphinized rabbits by ear vein with ouabain solutions to the end point of cardiac stoppage.<sup>21</sup>

TABLE III  
Preliminary Study of Effect of Rate of Injection and of Body Weight on the Lethal Dose of Ouabain in the Male Rabbit

Number of Rabbits	Injection Rate, mg. per kg. per min.	Mean Wt. in kg.	Mean Lethal Dose, mg. per kg.	Standard Deviations		Conclusions
				Wt.	Dose	
10	.001	1.59	.261	.20	.071	Effect of injection rate not marked
10	.002	1.87	.198	.28	.021	
10	.003	1.62	.242	.36	.042	Small rabbits relatively more tolerant than large
10	.004	1.75	.217	.24	.039	
10	.006	1.49	.238	.12	.056	
10	.008	1.68	.220	.32	.032	
10	.010	1.54	.243	.10	.047	
10	.010	2.65	.141	.22	.030	
10	.012	1.36	.246	.12	.038	
10	.016	1.61	.230	.19	.043	
10	.032	1.42	.304	.26	.045	Effect of weight obscured by that of injection rate
10	.064	1.42	.398	.26	.068	
10	.128	1.66	.628	.18	.071	
10	.256	1.77	.973	.32	.169	

A glance at table 3 shows that wherever there is an increase in the average weight of the rabbits in a group, the average lethal dose goes down, conspicuously so with the groups of small and large male rabbits on rate 10; on use of larger numbers of animals the difference became less conspicuous, but remained in the same direction. Table 3 also makes clear the increase in mean lethal dose at very rapid rates of injection. The main object was to investigate the effect on lethal dose of rate of injection, which has been found very important in determining the "cat unit."<sup>2, 67</sup> As frequently happens in research, we found something we were not looking for, a weight effect in this instance.

I was fortunate enough to be able to enlist the aid of Dr. C. I. Bliss in the analysis both of these rabbit data and of data obtained previously by Dr. B. J. Vos<sup>67</sup> at the University of Chicago on cats of both sexes and weights, 1.26 to 5.07 kg. Using the logarithms of the observed results and the method of Fisher,<sup>33</sup> sect. 29, it was found that the smaller animals were, in both species, relative to their weight, more tolerant of cardiac glucosidal preparations than the larger animals. The powers of the weight involved were as follows: 130 cats on digitalis  $0.89 \pm 0.06$ , less than 1.0, but not significantly so; for 61 cats on digitoxin  $0.77 \pm 0.08$ , and for 153 cats on ouabain  $0.79 \pm 0.05$ , both significantly less than 1.0. For 204 rabbits we found<sup>21</sup> the dose proportional to about the 0.6 power of the weight,  $W^{.573 \pm 0.058}$ , to be (a bit fussily) exact. Here the 0.058 is the standard deviation of 0.573, the difference from 1.0 is 0.427, and this difference is  $0.427/0.058 = 7.3$  standard deviation, from which we can calculate that the probability is less than 1 in millions of our being wrong in assuming that on the average small rabbits are, in proportion to weight, more tolerant of ouabain than large rabbits, at least within the experimental weight range, 1.02 to 3.64 kg.

It is interesting that Dr. Bliss<sup>8</sup> found in analysis of data obtained by Campbell in the silkworm that the larger silkworms were more tolerant of arsenic in proportion to their weight than the smaller animals, so that the size factor for time of death could be stated as  $W^{1.511 \pm 0.039}$ . Finding in the size factor an exponent greater than 1.0 is infrequent in the literature of the subject; the work of Falck on strychnine, however, supplies a parallel (figure 4). Dreyer and Walker<sup>25</sup> were impressed by finding in the standardization of diphtheria toxin in guinea pigs that "when the dose per 100 gm. of weight is made the same in light and heavy groups of animals of the same species the lighter animals survive for a much longer period than do the heavier. The explanation of this difference in death time is to be sought in a comparison of the doses calculated in relation to the surface. It is then seen that the dose thus calculated is much smaller in the lighter animals than in the heavier group." They reported<sup>25</sup> after examination of the literature that this was no isolated instance, and that "we have not up to the present met with any exception in the case of mammals and birds" to the general rule that smaller animals within the same species were in proportion to their weight more tolerant than larger ones. They list among the substances for which this appeared to hold good, either for effect on time of death or lethal dose (or possibly other effects) observations by various workers on arsenic trioxide, codeine, physostigmine and potassium chloride in the rabbit; various snake venoms in rats, rabbits, guinea pigs and cats; epinephrine and tetanus toxin in the mouse; and caffeine in dogs, cats and rabbits.<sup>25</sup> The methods of calculation are shown in considerable detail in a second paper.<sup>26</sup>

Dreyer and Walker<sup>25</sup> further point out that while examples can be found of greater tolerance per kg. to drugs or other toxic agents in small species,

e.g., the mouse, than in larger species, e.g., the guinea pig, the opposite phenomenon has also been observed (figure 4).

Clark<sup>16</sup> has recently reviewed the same subject. He appears to me, after examination of the references quoted, to be in error in his statement that "large mice are less susceptible than small mice to both neoarsphenamine and to aconite." Clark<sup>16</sup> has, I believe, in the case of aconite put a wrong

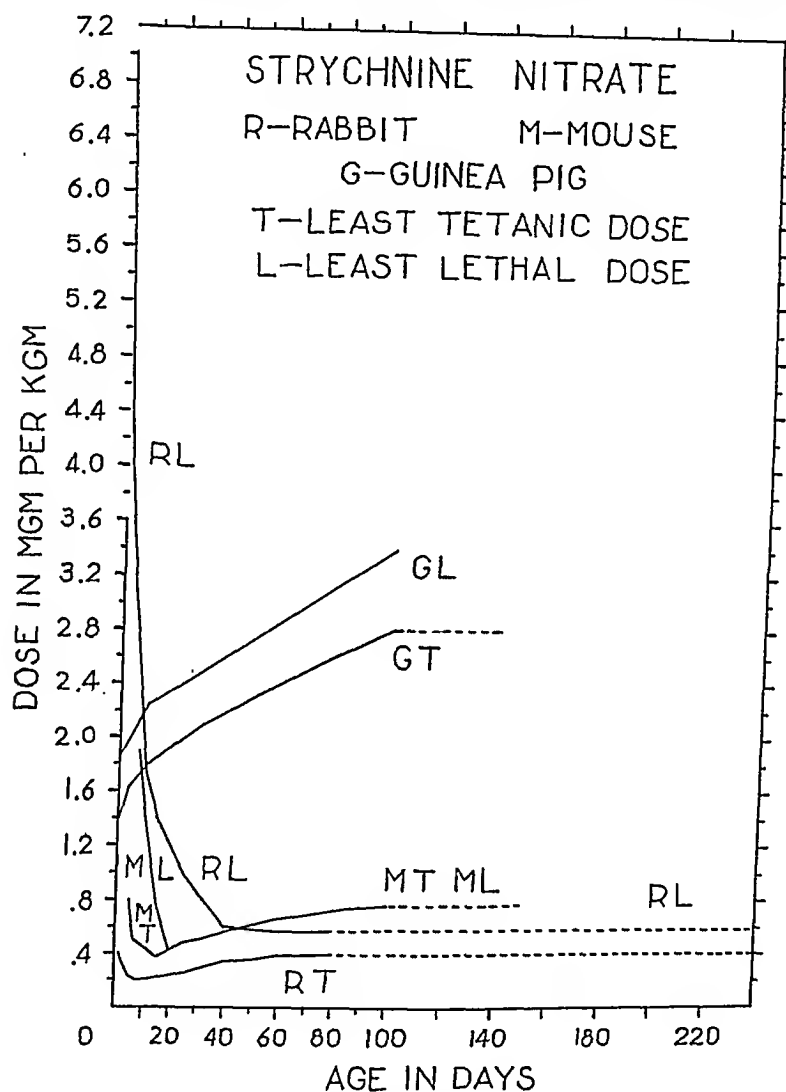


FIG. 4. In different species completely different relations between age and effective dosage of drugs may be obtained. Though mice are smaller than guinea pigs, their tolerance for strychnine is less in proportion to weight (Falck, 1884, 1885).

interpretation on a confusing report by Broom, Burn, Gaddum, Trevan and Underhill.<sup>12</sup> The conclusion drawn by the writer from study of this report is that the authors intended to state that they felt they had not established a significant difference in tolerance for aconite per gram, between small mice and large mice, the observed difference being considered a difference in colony resistance to aconite.

With regard to neoarsphenamine, which is given in somewhat larger dose per kg. to children than to adults, Durham, Gaddum and Marchal<sup>28</sup> state that "so far as our evidence goes, it would appear that, in immature mice, sensitiveness increases with age at such a rate as almost to neutralize the effect of increase in weight. On the other hand, in mature mice, from 20 gm. upwards, resistance apparently ceases to diminish at such a rate, so that some adjustment of dose by weight becomes necessary; and adjustment by simple proportion to weight seems likely to be as accurate in that range as that given by the use of any other formula."

If we have a definite end-point producible by a drug such as a measurable blood concentration of the drug, as with sulfanilamide, or rather sudden dramatic therapeutic improvement, as with digitalis in congestive heart failure, or fairly definite toxic symptoms, as with digitalis, or atropine, we can record the dose, daily, accumulated, or single, as the case may be, that was responsible in each patient for producing the result and by plotting against weight in various ways obtain some idea as to types of mathematical relation between weight and dose. A rather frequent finding, in view of fairly numerous references to dosage being properly proportional to various fractional powers of the body weight, appears to have been that plotting log dose against log weight gives results not significantly different from a straight line, at least over fairly considerable ranges of weight (figure 5). Where this is the case, the slope of the line is the power of the weight involved, and can be measured approximately from the diagram (vertical/horizontal intercept), or calculated by the method of least squares (Snedecor,<sup>64</sup> tables 6, 7).

A recent report on sulfanilamide by Long, Bliss and Feinstone<sup>50</sup> enables the calculation of mathematical relations between body weight and dosage advised to initiate or to maintain certain blood levels. Dr. Long has kindly pointed out that the same daily dosage may maintain different blood levels in the same patient, depending on whether or not there is restriction of fluid intake. The results of the calculations are shown in table 4 and figure 5. They suggest that therapeutically equivalent dosages of sulfanilamide are proportional to a power of the weight less than 1.0, and possibly around 0.5 to 0.8.

While logarithms are convenient for the mathematical analysis, their significance is not readily apparent. Use of figure 3 makes clearer just what is meant by proportioning dosage to powers of the weight. From this it can be seen at once, for example, that proportioning the dose to  $W^{-5}$  would mean that the average 100 kg. man (220.5 lbs.) should receive approximately 120 per cent of the adult dose (i.e., for 70 kg. weight). For estimating the power of the weight to which dose may be proportional, figure 3 is obviously not nearly so useful a type of device as figure 5, however.

The table of dosages used at Children's Hospital,<sup>15</sup> Iowa City, shows infants and children more tolerant of epinephrine in proportion to their



TABLE IV  
Relations between Body Weight and Therapeutic Dosages of Sulfanilamide in the Human Species

Information Used <sup>50</sup>							Therapeutic Dosage* Proportional to
Initial dose * used in establishing quickly a blood level of 10 to 15 mg. per 100 c.c., for weight of							
kg.	70	60	45	35	23	11	
dose, grams	4.8	4.2	3.6	3.6	3.0	1.8	$W^{.48}$
mg. per kg.	69	70	80	103	130	164	1.6
Daily total dosage * used in keeping up blood levels of 5 to 10 mg. per 100 c.c.							
kg.	70	60	45	35	23	11	$W^{.60}$
dose, grams	5.4	5.4	5.4	4.2	3.6	1.8	2.1
mg. per kg.	77	90	120	120	157	164	$W^{.74}$
Omitting first two dosages							3.2

\* Somewhat dependent on urinary excretion, and restriction of fluid intake.<sup>49</sup> Dose refers to total amount of drug, not to amount per kg.

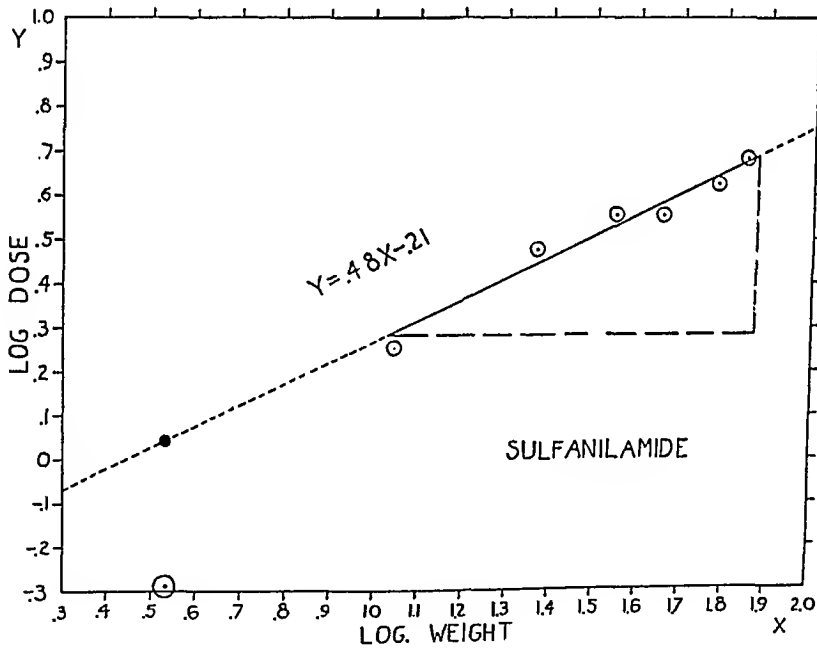


FIG. 5. Graphic test of linearity of relation of log (initial dose in grams of sulfanilamide used in bringing about a blood level of 10 to 15 mg. per 100 c.c.) to log weight in kg. The power of the body weight to which dose may be proportional is given by the slope of the solid line. Extrapolation to find the initial dose for a 3.4 kg. child gives the solid circle value, .04 antilog 1.1 grams; the extrapolation apparently fails, as Dr. Long<sup>50</sup> gives the desired dose as 0.51 grams (0.15 gram per kg.).

weight than adults. The hypodermic doses given are: at 6 months 3 minims (0.2 c.c.), at 18 months 4 minims, at 3 years 6 minims, at 5 years 7 minims, adults 7 to 15 minims (average thus 11 minims). Plotting a similar diagram to that for sulfanilamide in figure 5, the dosage of epinephrine comes out proportional roughly to the 0.6 power of body weight.

Bodansky and Duff<sup>9</sup> have found immature rats tolerate dosage of thyroxine rapidly lethal to mature rats.

The effective doses of digitalis in adults seem to be close to those necessary in children, and the daily maintenance dose in a child may be more than that required by the average adult. Withering<sup>69</sup> noted that nausea generally appeared, presumably in adults, when about 30 grains (1.94 gm.) altogether had been given. McCulloch and Rupe<sup>52</sup> gave children of 1 to 11 years with normal hearts doses of digitalis every four hours. Vomiting occurred after 4 to 20 doses in 17 out of 36. The amount required to produce emesis in these 17 cases averaged 17 c.c. of tincture, or 1.7 gm. of leaf, and assayed as 17 "cat units." The digitalizing dose for an adult averaged in Eggleston's series<sup>29</sup> about 2.2 gm. and in Pardee's<sup>54</sup> about 2.4 gm. in terms of good standard leaf of the time, of which 0.1 gm. was considered a "cat unit." (Incidentally, owing to recent change in U. S. P. standard for digitalis, a "cat unit" is now about 65 mg., apparently for a good standard leaf<sup>70</sup>; even more interesting, a "cat unit" is bigger if got by the 30 to 55 minute death times of the Magnus modification<sup>22</sup> of the cat method, which some use, than if done by using the death times around 90 minutes of the Hatcher-Brody method (Alday Redonnet<sup>2</sup>),<sup>40</sup> and less with ether anesthesia than with some other sorts,<sup>39</sup> and it is somewhat common for authors to omit to state what sort of "cat unit" they have.) Subject to these reservations, we may make tentative comparisons of doses for adults and children. The average 70 kg. adult may require about 33 mg. per kg. for digitalization. Jacobsen and Davison,<sup>42</sup> working with a group of children of 16 to 28 kg. (average 22 kg.) found the digitalizing dose of a leaf, probably of good standard potency,<sup>35</sup> average 1.7 gm., or 78 mg. per kg. To find the approximate power,  $P$ , of the weight to which the digitalizing dose of digitalis might be proportional, we may use the formula:

$$P = \frac{\log \text{adult dose} - \log \text{children's dose}}{\log \text{mean adult wt.} - \log \text{mean wt. of the children}}$$

$$= \frac{\log 2.3 - \log 1.7}{\log 70 - \log 22} = \frac{.36 - .23}{1.85 - 1.34} = .25$$

Turning to the question of daily maintenance dose of digitalis, we may use the following data. Jacobsen and Davison<sup>42</sup> found the maintenance dose for children average 200 mg. daily and Davison after further experience includes this figure in "The Compleat Pediatrician."<sup>18</sup> From Pardee's figures<sup>54</sup> the average for adults may be calculated as 111 mg.

Using the same formula as before:

$$P = \frac{\log 111 - \log 200}{.51}$$

$$= \frac{2.05 - 2.30}{.51} = \frac{-.25}{.51} = -.5$$

We thus reach the very interesting tentative conclusions, that the average "digitalizing dosage" of digitalis leaf is greater for children in proportion to their weight than for adults, and that the average daily maintenance dosage for children of about 22 kg. average weight is not only greater than that for adults in proportion to weight, but greater in absolute figures. The digitalizing dosage may be proportional to  $W^3$  approximately, and maintenance dosage of  $W^{-5}$  approximately. Figure 3 does allow here of estimating these powers directly, since there is only one point to plot in each case, the second being always at the "big intersection," simply by plotting percentage of adult dose ( $x$ ) against child weight and taking as the power that for the nearest curve. These are very rough estimates, from admittedly inadequate data, but it is hoped they will stimulate further observations.

Eggleston<sup>29</sup> and Pardee,<sup>54</sup> who worked with adults, and Jacobsen and Davison<sup>42</sup> from experience with children, found no outstanding relation between dosage and body weight within their groups of patients. This may have been due to the small numbers of cases worked up, and to natural variability of results, enhanced by use of different preparations (biologically standardized) in different groups of patients.

Dreyer and Walker<sup>25, 26</sup> seem to have overlooked Falck's early (1884, 1885) observations,<sup>32</sup> to which Clark<sup>16</sup> draws attention. Falck<sup>32</sup> made observations on the effect of age on least observed tetanic and lethal doses of strychnine during at least the first 100 days in the life of the guinea pig, mouse and rabbit. The results are shown in figure 4. The least observed lethal dose per kg. for the rabbit was highest at birth and diminished rapidly, indicating a size factor less than 1.0. The tetanic doses for the rabbit and mouse, and the lethal dose for the mouse at first diminished with increasing age, and then increased, apparently reaching eventually a plateau. Both the tetanic and the lethal doses per kg. for the guinea pig increased from birth on for at least 100 days; in the rapidly growing guinea pig, which has a more advanced neuromotor mechanism at birth than either mouse or rabbit, there seems thus to be clearcut evidence of a size factor greater than 1.0. The evidence from animal experiments is hence somewhat contradictory, but is certainly such as to make one very cautious about giving strychnine to children. Strychnine is not important as a drug for children, but Aikman<sup>1</sup> says, "strychnine poisoning with brightly colored sugar-coated cathartic and tonic tablets causes more deaths in children than any other poison" (see also Priest<sup>59</sup>). The lethal dose for a child may be very small; a boy of 3½ years has been killed by a dose estimated as 2 or 3 mg. (gr. ⅓₂ or ⅓₂₀)<sup>48</sup>; an adult has been killed by 36 mg., or a little over ½ grain of strychnine hydrochloride.<sup>48</sup>

It is of particular interest to consider next the size factor for barbiturates, among which are apparently the most effective strychnine antidotes. Clear clinical reports have established the life-saving value of sodium amytal<sup>43, 59</sup> and pernoston,<sup>44</sup> and the prompt cessation of the painful and

potentially traumatizing<sup>14, 20</sup> strychnine convulsions when these drugs were given by vein in human cases. A number of other barbiturates, especially<sup>3</sup> pentobarbital (nembutal), when given by vein have been found in the laboratory to suppress strychnine convulsions,<sup>19, 20</sup> and the antagonism is demonstrable even in the spinal cat.<sup>58</sup>

Barbiturates are generally considered well tolerated by children. Clark<sup>16</sup> found the results of Bazett and Erb<sup>6</sup> on the anesthetic dose of pentobarbital in cats and dogs to follow the relation approximately  $W^{.67}$ , though Bazett and Erb<sup>6</sup> did not consider so simple a relation sufficient. Donald and Raventos<sup>24</sup> have recently reviewed the somewhat contradictory literature on the size factor for barbiturates. The need for caution during the early days of life is emphasized by their report on the barbiturate sodium evipal. Giving 20 mg. per kg. by vein in pigs, they found the duration of narcosis in pigs six months old averaged about 20 minutes, in those 10 to 80 days old about 12 minutes, but in pigs two to four days old rose to 50 minutes. The new-born were thus highly susceptible; the higher susceptibility wore off at about 10 days of age and began to rise somewhat at about three months of age. There was considerable variability among individuals of the same age. Percy and Weaver<sup>55</sup> considered that old dogs as well as young dogs were less tolerant of barbital than dogs of intermediate age, which emphasizes sensitiveness at both ends of the age scale.

Comparing Falck's results with strychnine<sup>32</sup> (figure 4) with those of Donald and Raventos<sup>24</sup> with sodium evipal, one finds Clark's conclusion<sup>16</sup> inescapable: "at present it is impossible to enunciate general laws regarding the relation between dosage and body weight, since completely different relations appear to be obtained with different drugs," and, one may add, in different species.

Why children require or tolerate in proportion to their size higher dosage of some drugs than do adults cannot at present be explained. Dreyer and Walker<sup>25, 26</sup> considered blood volume which they found proportional to surface area, or about  $W^{.72}$ , of paramount importance. One must, however, take into account several other possible factors, such as larger proportionate average basal metabolic rate, daily urinary output, and weight of liver and other organs concerned with destruction or conjugation of drugs.

The liver in a man 20 to 30 years of age averages, according to Roessle and Roulet,<sup>62</sup> 1587 grams; in a woman, 1371 grams, or 86 per cent of that of the male. Assuming a drug to be entirely destroyed in the liver, and livers to have the same destructive capacity per gram liver tissue at all ages, the new-born, with livers averaging 78 grams, according to Coppoletta and Wolbach,<sup>17</sup> would tolerate about 5 per cent of the dose for the adult male, or substantially the proportionate dose indicated by their body weight, according to the weight rule (figures 1, 2). Several authorities give much higher liver weights at birth than 78 grams, but this figure of Coppoletta and Wolbach<sup>17</sup> has been preferred, since they definitely excluded livers showing pathological changes. The average liver weight increases at first slightly

and later definitely more rapidly than the body weight, so that using the same table<sup>17</sup> of liver weights we should give a dose at six months of 13 per cent, at two years 25 per cent, at six years 40 per cent, and at 12 years 58 per cent of adult dose, all somewhat in excess of the proportions indicated by the weight rule of figures 1 and 2, but not so great as those indicated by surface area. Thus, in children the somewhat disproportionately rapid growth of the liver may possibly be a factor in increasing tolerance to some of the drugs, such as quinine, barbitol and phenobarbital, which are partly destroyed or detoxicated in the liver, to the more unstable barbiturates which are almost wholly destroyed in the body, and to arsphenamine, the arsenic from which is excreted chiefly by way of the bile into the feces.<sup>65</sup>

In the case of sodium and ammonium mandelates used therapeutically, the daily dose is sometimes given as 1 gram per 100 c.c. of previous 24 hours urine, the object being to obtain urinary concentrations of 0.5 to 1.0 per cent of the drug. This may work out at about 4 grams for an infant, whose urine volume may average 400 to 600 c.c.,<sup>46</sup> and practically adult dose of 12 grams for a 12 year old child, whose urine volume may average 1200 to 1500 c.c.,<sup>46</sup> quite in the adult range. This factor also affects the dosage of sulfanilamide, the dose of which is sometimes given as "for adults  $\frac{1}{3}$  grain, for infants 1 grain per pound of body weight." In proportioning dosage of drugs on the basis of urinary output, it should be remembered that the fluid intake during the first day of life may be only a few c.c., during the second day only about 100, the third 250, the sixth 400, the fourteenth 500 c.c.<sup>57</sup>; even assuming about 40 per cent of this to appear as urine, the volume seems insufficient to permit any great amount of drug excretion through the kidney during the early days of life. The 24-hour urine volume is, moreover, subject at all ages to tremendous fluctuations<sup>45</sup> from day to day, being affected by fluid intake especially, by temperature of air and body, humidity, clothing, diet, etc. The lungs and skin always have primary liens on the water provided in ingested food and drink. The extraordinary variability of basal 24-hour urinary volume in c.c. is well illustrated by coefficients that have been given for calculating this as averaging 1000 times surface area (table 1), but with a minimum coefficient of 400 times and a maximum of 1500 times.<sup>61</sup> Thus, for a boy of 9 years of age the basal 24-hour urine might average 980 c.c., but vary from 390 to 1470 c.c., or even larger amounts with excess fluid ingestion. The high average ratio of urinary output to body weight suggests that older infants and children should have, as a rule, a very good tolerance for many drugs excreted largely or chiefly through the kidney,<sup>65</sup> such as quinine, phenobarbital, bismuth, mercury, atropine, mandelic acid, sulfanilamide. We should expect the new-born on the other hand to be rather sensitive to drugs excreted mainly in the urine.

The antimalarial dosage of quinine sulfate suggested by the Malaria Commission of the League of Nations<sup>38, 51</sup> is 1.0 to 1.2 grams (15 to 18 grains daily) and recently by the U. S. Public Health Service 20 grains (1.3 grams) daily. An article by Ross and Alcock<sup>63</sup> says of quinine "children

can be given a larger proportion by body weight than adults, say twice as much." On this basis a child of 12 with malaria would be given the adult dose, say 1.0 gram, daily; at 5 years 0.5 gram daily, and 1 year 0.2 gram daily; Pfaundler and Schlossmann<sup>57</sup> recommend 0.01 gram ( $\frac{1}{6}$  grain) quinine hydrochloride per month from 4 to 12 months of age as daily dosage; larger doses are recommended by some other workers.

The barbiturates are partly detoxicated in the liver and partly excreted in the urine.<sup>65</sup> With barbital 75 per cent and with phenobarbital 10 to 40 per cent may appear in the urine unchanged, with the newer and briefer-acting less or none. Children are generally considered to tolerate phenobarbital very well, which is perhaps explicable on the basis of somewhat higher proportion of liver tissue and greater urinary output. On the other hand, the same reasons would cause one to think that strychnine should be well tolerated by children, and the evidence rather points to strychnine being even more dangerous in children than in adults.

### DISCUSSION

There seems to be enough evidence available to show that it is not sufficient to teach that dosage of drugs for children should be determined by direct proportion to weight, or by use of simple rules. The main points to emphasize are (1) giving careful attention to actual good pediatric practice, (2) noting that there is no quantitative rule at present, or likely to be developed in the future, that will fit all drugs, (3) recognition of the fact that the child's dosage of some important drugs is much less different from the adult's than would be expected on the basis of a direct proportion to body weight, (4) acquisition of an attitude of humble enquiry in view of the fact that the basic quantitative data that might serve as a basis for dosage rules are, in the case of many drugs, not yet available in any systematic form.

Toward the end of the natural term of life, with basal caloric output falling, and with a decline in size of liver<sup>62</sup> and kidney,<sup>68</sup> caution in giving drugs is obviously necessary. But individual variability still plays a rôle, so that it may be necessary finally to use rather large doses of drugs in order to secure the desired effects, even in a little old lady. In short, after all this discussion, the only principle of dosage that survives is that the dose must be adjusted to the individual patient, and that nothing can or will supersede clinical experience, and careful study, combined with good judgment.

### CONCLUSIONS

1. Laboratory observation has shown that the effective, usually lethal, doses of various drugs are usually less per kg. in the larger animals of a species than in the smaller. This is an over-simplification; a species may show either high resistance or high susceptibility at birth, with possible decrease for a few days or weeks, followed by increase.

2. On the basis of clinical observation the therapeutic dosage of atropine, the arsphenamines, bismuth, digitalis, mandelic acid, some mercurials, sulfanilamide and some other drugs, has been set at somewhat higher levels in proportion to weight for infants and children than for adults. On the other hand, dosage of morphine or strychnine, even in direct proportion to body weight, appears too great for safety of some individuals, and caution is in order until, at least, the susceptibility has been determined, especially in the case of an infant, child or aged person.

3. The greater tolerance of the young for some drugs may be due to various factors, possibly including proportionately larger average (1) surface area, (2) basal metabolic rate, (3) liver weight, (4) daily urinary volume.

4. The inevitable excretory and metabolic readjustments in the first few days or weeks of extrauterine life, as well as the decline in metabolic rate, reduction in size and possible pathological changes in liver and kidney after middle life (especially in old age) enjoin caution in the use of drugs during these periods.

Charts have been prepared to show the relative doses provided by various rules based on age, weight to various powers, surface area, and basal caloric output.

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## ADENYLIC ACID IN HUMAN NUTRITION \*

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FROM our studies of a large series of persons with mixed vitamin deficiency, we reported recently<sup>1, 2, 3</sup> that the diagnostic manifestations of pellagra, beriberi, riboflavin deficiency, vitamin A deficiency and vitamin B<sub>6</sub> deficiency respond to the administration of large amounts of synthetic nicotinic acid, thiamin hydrochloride, riboflavin, oleum percomorphum, and synthetic vitamin B<sub>6</sub> respectively. Each of these active chemical substances, in addition to its specific action for the relief of certain characteristic symptoms, promotes a general sense of well-being in these persons. Following the administration of crystalline vitamin supplements to their inadequate diets, the patients often became strong enough to work, with the result that a more adequate diet was subsequently bought and eaten. If the diet was not improved and these synthetic substances were added as supplements, better health followed, but many patients remained poorly nourished and continued to have symptoms. This suggests that even though these essential substances—nicotinic acid, thiamin hydrochloride, riboflavin, oleum percomorphum or carotene-in-oil, and vitamin B<sub>6</sub>—are supplied, the diet is still deficient in another substance or substances. Since it has been shown in this clinic<sup>4</sup> and also by Sydenstricker, Geeslin, Templeton and Weaver<sup>5</sup> that riboflavin, in addition to its specific effect in the treatment of clinical riboflavin deficiency, is beneficial to certain pellagrins in relapse, and since so many of these "specific" deficiencies are clinically interrelated, it is possible that the same general biochemical system or systems may be disturbed. Adenylic acid is a constituent of the pyridine dinucleotides, coenzymes I and II, and is widely distributed in nature. It is intimately concerned with carbohydrate and protein metabolism. Therefore, we decided to investigate the properties of adenylic acid by administering it to normal persons and to persons with mixed deficiency disease.

Adenylic acid † was administered intravenously to eight normal persons, in doses of from 3 to 20 milligrams, dissolved in sterile physiological solution of sodium chloride. Within 15 to 30 seconds after the injection was begun, the subjects had an involuntary deep gasping inspiration, and complained of a burning and nervous "fluttering" sensation in the upper part of the abdomen and a feeling of fullness in the head. Oftentimes they

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† Three preparations of adenylic acid were furnished through the courtesy of Anheuser Busch, Inc. and Merck and Company.

stated that they were dizzy, and sweating of the forehead was observed in some of the subjects. Four of them had *angor animi*. All of the patients had transient flushing of the neck and face. The pupils became widely dilated; frequently there was blinking for several seconds. The arterial blood pressure fell slightly and the heart rate increased. All symptoms vanished within three to five minutes after they began, and there was no evidence of harmful effects. The possibility of impurities in the adenylic acid used is being investigated. The administration of a single dose of 200 milligrams of adenylic acid by mouth produced similar but less intense symptoms in about one-fourth of these persons, and some complained of headache. A similar oral dose, repeated every hour for five hours, did not increase the severity of these symptoms. Adenylic acid is only slightly soluble in water, but dissolves readily when incubated with normal human gastric juice. No toxic symptoms were observed when such gastric juice preparations were administered by mouth.

Group I. Two patients with pellagra in relapse were given 500 milligrams of nicotinic acid\* daily as a supplement to their extremely deficient diet. This diet was unchanged during the period of observation. The immediate response to nicotinic acid was dramatic but after a period of six weeks, gradual relapse occurred. The daily dosage of nicotinic acid was doubled and another, but less dramatic remission was induced. The patients, however, did not remain symptom-free on this additional dosage. After diagnostic lesions of pellagra returned, 500 milligrams of adenylic acid were administered daily for three days, while the dosage of nicotinic acid remained constant. Dramatic relief of the symptoms occurred and the signs of pellagra once more disappeared in these two patients.

Group II. The second group consisted of seven patients with typical pellagrous glossitis and dermatitis. Each of these patients received 1000 milligrams of adenylic acid in divided doses for one day. Within 24 hours, the burning sensations in their tongues disappeared and they experienced a general increase in strength and sense of well-being. The glossitis and dermatitis, however, improved slowly and, in one case, not at all. When improvement occurred, it was gradual in contrast to the rather abrupt and dramatic relief of the mucous membrane lesions of pellagra following nicotinic acid therapy or the relief of the painful symptoms of beriberi following treatment with vitamin B<sub>1</sub>.

Group III. This group of six patients, who had subsisted on grossly deficient diets for many years, had intense burning of the oral mucous membranes and, in some instances, of the skin. No diagnostic skin or mucous membrane lesions of pellagra were present. After failure to relieve these symptoms by means of placebos or nicotinic acid, 1000 milligrams of adenylic acid were administered orally, in divided doses of 100 milligrams

\* In the presence of nicotinic acid amide or nicotinic acid, we have observed the *in vitro* synthesis of coenzymes I and II by defibrinated blood, but similar studies using pyrazine monocarboxylic acid gave no evidence of *in vitro* synthesis of these enzymes.

each, for one day. This was followed by immediate cessation of the symptoms. No return of burning was noted but this study was ended during the period when the diet was improved by summer crops.

These studies indicate that some of the symptoms of mixed vitamin deficiency are relieved by adenylic acid. This compound, in some cases, may act in a manner similar to riboflavin in increasing the effectiveness of nicotinic acid in pellagrins in relapse. This finding gives further evidence not only of the multiple and mixed nature of these dietary deficiency diseases in human beings but also suggests that they are the result of dysfunction of certain fundamentally related enzyme reactions. Because of the severe reactions produced by intravenous injections of all preparations of adenylic acid we have used, we do not recommend that this compound be administered to human beings until further studies are made. Investigation along these lines is in progress.

#### SUMMARY AND CONCLUSIONS

1. Pellagrins in relapse are benefited by treatment with nicotinic acid and adenylic acid.

2. Six patients with malnutrition, who had intense burning of the oral mucous membranes, but no diagnostic evidence of pellagra, were relieved following treatment with adenylic acid alone.

3. Since severe reactions were produced by the intravenous injection of three preparations of adenylic acid, we do not recommend that this compound be administered to human beings.

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# VARIATION OF BLOOD PRESSURE WITH SKELETAL MUSCLE TENSION AND RELAXATION.

## II. THE HEART BEAT \*

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IN previous studies <sup>1, 2</sup> systolic and diastolic pressure were measured in man, lying at rest, at intervals beginning about 15 minutes after reclining, while potentials were recorded (in microvolts within the frequency rate, 30–4000) from electrodes in one or more of the following groups: the flexor muscle in the right upper arm, the left quadriceps femoris muscles, the abdominal muscles, muscles in the region of the right eye. Apart from fall of pressure following soon after and attributable to change to the recumbent position, there were indications that the blood pressure variable is a function of skeletal muscular tension. Prolonged lying down did not in itself induce further lowering of pressure; in fact the pressure remained at about the same level or increased unless the subject relaxed. The data suggested that the ratio or decrement of pressure to decrement of muscular voltages, as recorded, was often greatest when the muscular voltages dwindled toward zero ( $V_m \doteq 0$ ).

One factor in the chain of events leading to fall of blood pressure attendant upon skeletal muscular relaxation may be diminished rate and force of the heart beat. This possibility can be tested with the data at hand.

On many of the myograms made at the same time as the blood pressure tracings, small electrical records from the heart can be clearly distinguished, permitting the heart rate and the heart voltage there to be determined. More precisely expressed, the electrocardiogram indicates the potential differences in electrodes located about 4 to 6 cm. apart in the arm or the thigh or the abdominal wall at a constant distance from the heart.

It must be admitted without reserve that the character of the QRS curves in the electrocardiograms of two individuals does not enable us to compare the force of beat in their hearts. Even in the same individual observed from day to day, the QRS curves admittedly would afford no basis for comparison concerning the force of the heart beat on different occasions, since the heart might shift in position in the chest and other essential conditions might vary also. These considerations should not obscure the possible value of the QRS curve in affording comparative data in the same individual concerning the force of his heart beat, *provided that essential conditions remain constant.*

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Einthoven and Hugenholtz,<sup>3</sup> answering many authors inclined to separate the mechanical and electrical phenomena of the heart beat, afforded their classic demonstration in 1918. Using a sensitive mechanical recording device, they found that in heart muscle poisoned with KCl solutions mechanograms could be secured so long as the electrocardiograms persisted. "All our experiments with poisoning, injury or removal of indispensable constituents have given us the same result, namely, a complete parallelism of the mechanical and electrical phenomena, always changing *pari passu*" is the statement of Einthoven in his Harvey Lecture (1924-25). Professor H. B. Williams has observed a patient evidently showing progressive muscular atrophy of the heart whose QRS curves declined accordingly (personal communication). He states his experience as follows:

"If you find in a new patient never before observed an electrocardiogram which looks very much like a normal one except that all is uniformly reduced, it may indicate general impairment of the myocardium and *it may not*. Some people have much lower voltage than average as a personal peculiarity. Such an EKG with a history of progressive narrowing of the field of cardiac response and a status praesens of shortness of breath on slight exertion with no valvular defects or anemia, I should regard as confirmatory of a tentative diagnosis of myocardial disease.

"If, however, you see a patient over a period of months and see the electrocardiogram progressively shrinking while maintaining its general form and with the shrinking of the EKG there is clinical evidence of diminishing effectiveness of the heart and valvular lesions are not present to complicate the situation, I regard it as proof positive of general myocardial disease."

The harmonious conclusions of Einthoven and Hugenholtz as well as Williams afford basis for the view that voltages in electrocardiograms are functions varying with the heart beat and that their magnitudes will enable us to compare force of heart beats in the same individual, provided that essential conditions will remain constant. We can assume that the presence of muscular contraction, however slight, will be denoted by action-potentials (Fulton,<sup>4</sup> Jacobson,<sup>5</sup> Davis and Davis<sup>6</sup>).

In the present studies, these conditions are met, because comparisons of voltages are made only in the same individual in a particular period of rest (60 to 90 minutes), while the electrodes remain in a constant position inserted in the tissues. It is an essential condition that the individual does not shift his position during these periods; even the limbs lie unmoved. Accordingly, in most or all instances, the position of the heart in the thoracic cavity may be assumed to be practically constant throughout. Therefore, it seems warranted to assume that in a particular individual during a specific experimental period, we can here follow the variations of force of the heart beat by measuring the heart voltages at corresponding instants.

The peak voltages measured in the present records differ from the QRS

of the electrocardiogram as commonly recorded with the string galvanometer in that the two electrodes are but 4 to 6 centimeters apart, both residing in the arm or in the abdominal wall. Under these conditions, I believe, the electrocardiogram shows much less variation during any single respiratory cycle than with the leads in their customary positions. This renders it unnecessary to make certain that the electrocardiograms to be compared occur always in the same phase of the cycle of respiration. A second difference results from the fact that the present electrocardiograms are recorded by means of amplifiers, transformer coupled. Amplification is required because the differences in potential marking the QRS curve, if recorded from electrodes only 4 to 6 centimeters distant from each other, as in one limb, must be measured in microvolts.

In 28 records it is readily possible to distinguish the electrocardiograms. The mean of several voltages was commonly taken as corresponding with each blood pressure tracing, since the latter was coincident with several heart beats. Accordingly we compare not one heart voltage with another, but the arithmetic mean of several heart voltages taken at the time of one pressure tracing with those taken at the time of another.

The results were not anticipated. There is in general a striking correspondence between fall in blood pressure and simultaneous decline in heart rate or in heart voltage or in both. In every instance (18 out of 28) where both systolic and diastolic pressure fall, there occurs a fall also in heart rate or in heart voltage or in both (10 out of 18). In the 18 instances mentioned, the fall both in systolic and in diastolic pressure averages about 9 mm. mercury, the decline in heart rate approximates 7 per minute and the diminution in heart microvoltage averages about 1.0 (table 1).

It seems reasonable to believe that a fall of 9 mm. blood pressure as an average is a significant figure; the more so, since this figure is added to the decline occurring upon lying down, so that the sum of the two falls constitutes an important fraction of the original pressure. (In order to eliminate subjective errors in taking blood pressure, the Tycos self-recording sphygmomanometer was used in these studies. The point of systolic pressure is sharply indicated on the charts made with this instrument; but there is question at times concerning the reading of the diastolic pressure. Accordingly we may believe that the figures for systolic pressure have a negligible error, but no such assumption is made regarding those for diastolic pressure. However, since all the readings were made by one person, we may assume that errors, if any, were in the same direction, and that the results for diastolic pressure are satisfactory at least for purposes of comparison.) The 28 records in question, as will be seen, include instances in which blood pressure did not fall. They also include instances in which action-potentials from the muscles in the arm or thigh or abdomen did not decrease; for in the present article, unlike the preceding one, we are not examining the possible correlation of changes in these potentials with changes in blood pressure.

A statistical analysis indicates clearly that the results are not due to



TABLE I  
Changes in Heart Rate and Heart Voltage, Coincident with Changes in Blood Pressure

Subject	Age	Sex	Blood Pressure	Heart Rate	Heart Voltage
Ny.	20	M	-2/-5	-5	-0.8
Ad.	20	M	-5/+2	-3	-1.7
Ba.	22	M	-7/-13	0	-0.3
Et.	51	M	-7/+1	-3	-0.3
Et.	51	M	-12/0	-3	-0.3
Ro.	24	M	-18/-11	-12	-0.8
Ka.	30	M	-12/-18	-19	0
Lu.	27	M	+3/0	-4	0
Di.	37	M	-10/-5	0	-0.9
Ve.	35	M	-19/-25	-6	-0.3
Ve.	35	M	+1/-5	-2	0
Bn.	40	M	-1/-6	-12	+0.3
Bh.	35	M	-25/-2	-4	-1.4
Ma.	61	M	-7/-16	-5	-0.4
Ja.	24	M	+3/-2	-20	0
Adl.	20	M	+2/+9	-18	+0.3
Fl.	24	F	-2/-9	-4	-1.2
Ri.	18	F	-5/-6	-4	0
Od.	26	F	-5/-12	0	0
Mu.	23	F	-3/-1	-9	+0.3
Sh.	20	F	-4/-9	-12	-0.8
Ba.	22	F	-6/-1	+2	-0.4
Wi.	23	M	-2/0	0	-1.7
Eik.	24	M	-23/-10	-9	-5.7
Ga.	23	M	-11/-8	-15	-1.4
Bo.	28	M	0/-3	-9	-0.3
Th.	?	F	0/-1	0	+0.1
Ed.	20	M	-9/-9	-6	-1.4

chance variation. The following summary has seemed most simple and is modified on suggestions for which I am indebted to Professor Walter Bartky. In any one of the 28 records considered, coincident changes respectively in systolic pressure, diastolic pressure, heart rate and heart voltage are possible in 16 varieties. As indicated in table 2, let  $W_1$  represent

TABLE II  
Statistical Analysis of Table 1;  
Possible Coincident Changes in 4 Variables  
Systolic Pressure, Diastolic Pressure, Heart Rate, Heart Voltage

$W_1$	$W_2$	$W_3$	$W_4$	$W_5$
- - - -	- - + - - - - +	+ - - - - + - - + + + - + + - + + - + + - + + +	+ + - - + - + - + - - + - + + - - + - + - - + +	+ + + +
Scores <sup>1</sup>				
		Random	Actual	
$W_1$		1.75	13.50	
$W_2$		3.50	6.00	
$W_3$		10.50	6.00	
$W_4$		10.50	2.50	
$W_5$		1.75	0.0	

<sup>1</sup> In scoring, it is necessary to consider zero as midway between minus and plus and to credit the value. 1/2 to  $W_1$  or to  $W_2$  or to  $W_3$  as the case may deserve.

— — — —,  $W_2$  represent — — + — and — — — +, while  $W_3$ ,  $W_4$  and  $W_5$  represent the other groups of combinations there shown. We are particularly interested in  $W_1$  and  $W_2$  but most of all in  $W_1$ , the instance in which there is decrease in systolic and in diastolic pressure accompanied by decrease also in heart rate and heart voltage. The chance score for  $W_1$  would be  $\frac{1}{16}$  of 28 = 1.75. Actually we find that  $W_1$  occurred 13.50 times. Obviously this result differs very greatly from the purely random score stated above; so much so that it seems superfluous to determine the probability figure. The same can be said regarding the actual score of  $W_1 + W_2 = 19.50$ , compared with the random score of  $W_1 + W_2 = 5.25$ .

In the score of 28 instances considered, decreased systolic plus diastolic pressure occurs in 20 instances. Most of these 20 instances are accompanied by decrease both in heart rate and in heart voltage (13.5 out of 20); all of these 20 instances (except one half of one, as scored) are accompanied by decrease at least in heart rate or in heart voltage.

Obviously, decline in the force of beat (represented by voltage, in the present instances) or decrease in the rate, while the strength remains approximately the same, indicates relaxation in the cardiac musculature; more precisely stated, indicates less effective or fewer beats during a given period of time.

Is the recumbency in itself responsible for the lowering of blood pressure and also of the diminished heart rate and heart voltage? This question was answered negatively in the preceding article; for during about 15 minutes after the change from sitting or standing, there occurred an initial fall, but no further decline in pressure upon prolonged recumbency, unless relaxation increased during the period. Accordingly we infer that cardiac relaxation tends to accompany relaxation in the skeletal musculature and that this should be taken into account in explaining the blood pressure fall which tends to occur in an individual lying down, if and when contractions in his skeletal muscles diminish.\*

In two subjects (Th and Ve, figures 3 and 5, loc. cit.) blood pressure shows no significant fall. Do the heart rate and heart voltage decline in these instances as they generally do in those where the fall in pressure averages about 9 mm.? In Th, taking the initial pressure as  $121\frac{1}{76}$  mm. of mercury and the pressure after the attempt to relax (which met with failure) as  $121\frac{1}{75}$ , the pressure remains practically the same. So also does the pulse rate—100 both times. The microvoltage from the heart remains practically constant, namely 7.4 and 7.5 at the two times. In Ve, while relaxing, the pressure is  $101\frac{1}{59}$  initially, changing to  $102\frac{2}{54}$  after 45 minutes further relaxation. This change is so slight as to lie within the probable limits of error in taking and reading the pressure, so that it may be regarded as practically an equality. Correspondingly, the heart rate varies insignificantly, namely,

\* In the 20 instances considered above, relaxation in the skeletal musculature is inferred rather than demonstrated to be concomitant with the cardiac relaxation. Checking on this correlation will be considered in a later article.

from 62 to 60, while the heart microvoltage is initially 2.0 and does not change from this value. In short, the heart rate and heart voltage do not decline significantly in these two instances where blood pressure also does not decline during the period of recumbency. Accordingly these data for heart rate and heart voltage permit us to believe that under the present conditions variation or constancy in blood pressure depends (among other factors) to a noteworthy extent on corresponding variation or constancy in the force (voltage) and rate of the heart beat.

#### COMMENT

Assuming that blood pressure tends to vary with skeletal muscle tension (en masse or perhaps preponderantly with tension in certain groups, such as the abdominal muscles), there evidently are various other possible physiological mechanisms. One would be relaxation of muscle fibers in the arterioles and in the muscular arteries—a diminution of vascular tonus. This would be analogous to relaxation in other visceral muscle tissue, notably in the lowermost portion of the esophagus, which, as I have shown, can occur upon relaxation of the skeletal musculature. Our present knowledge is insufficient to permit us to say by what channels this relaxation of arterial musculature might be effected, but there are four plausible hypotheses:

1. The contracting fibers stimulate sensory end-organs in the muscle spindles, arousing afferent impulses which proceed to excite nerve-centers in the cord or perhaps even in the brain, which exert pressor influences by way of the sympathetic nervous system. Relaxation reduces this stimulation at the source and so effects a reduction of pressure.

2. Possibly skeletal muscle contraction, even in minimal degree, is accompanied by secretion of a pressor substance by some gland such as the suprarenal, or by some other organ, or possibly,

3. The pressor substance comes during contraction from the neuromuscular junction (acetylcholine) or from the muscle tissue itself, then passing to the blood stream.

4. Skeletal muscle contraction in intact man occurs only along with activities in divers portions of the nervous system. At least a portion of the somatic motor system participates whenever we perform an involuntary as well as voluntary act. Commonly what takes place is brain-cord-efferent nerve-muscle-afferent nerve-cord-brain-cord etc. action. In this recurrent chain of acting tissues, we are accustomed to assume that the brain is the first to act, but it is by no means certain that this traditional view is entirely justified. This leads to the consideration that the influence on blood pressure may be initiated in one or more of the various regions which take part in the total act of voluntary or involuntary contraction as above defined. Perhaps one region of such initiation is in the cortex. Evidence has recently been furnished by Hoff and Green<sup>7</sup> that nerve elements controlling blood pressure exist in the cortex adjacent to somatic motor centers.

## SUMMARY AND CONCLUSIONS

1. If, in man, beginning about 15 minutes after lying down, there occurs sufficient decline in skeletal muscular action-potentials, a fall in systolic and diastolic pressure characteristically takes place also (*loc. cit.*). Under these conditions, or if, at least, no marked increase in muscular action-potentials occurs, a decrease in cardiac voltage and rate, or in one of them, attends the fall in pressure. The data are insufficient to test whether there is parallelism between the curves of action-potentials from skeletal muscles and from cardiac muscles.

2. Fall in blood pressure upon skeletal muscle relaxation presumably depends upon relaxation in muscle fibers of the circulatory system, notably in the arterioles, in the muscular arteries and perhaps in the heart, but possibly, also, relaxation in the muscle beds containing capillaries is a factor. Precisely what physiological channels are involved has not been determined, but possibilities are discussed. Measurement of the heart rate and heart voltage approximately simultaneously with the blood pressure reading affords data which indicate that one factor presumably effective in the observed fall in pressure during protracted muscular relaxation is diminished force and rate of the heart beat. In some instances where relaxation remained constant and the blood pressure did not change markedly, the heart rate and voltage also remained practically unaltered.

3. The results suggest that, upon lying down, even individuals with "normal" blood pressure commonly show heart action a little faster and more forceful than would occur if they were more relaxed in their skeletal musculature. They suggest also that in "essential" hypertension the heart muscle may be unnecessarily "tense," showing, even when at rest, a somewhat excessive rate and voltage, as compared with lower values attained if the individual is considerably more relaxed.

4. The findings furnish some additional foundation for the view that high blood pressure in "essential" hypertension can result in part from habitual activity involving hypertensive states in the skeletal musculature.

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## LIMITATIONS OF RENAL FUNCTION DETERMINATION \*

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THE improvements in biochemical methods have given great impetus to the use of the clinical laboratory by physicians. Procedures which were originally interesting laboratory confirmations of diagnostic impressions of an alert physician at the patient's bedside, later became routine studies on hospital patients. The precepts of pioneers in the use of laboratory tests have led to the increasing application of such procedures in accepted medical practice. It seems logical to utilize all possible aids in obscure and chronic disease, particularly for their benefit in preventive medicine.

As the biochemist strives to devise methods for the measuring of physiologic function in various organs of the body, a disconcerting diversification in the abilities of any organ becomes apparent. The as yet innumerable functions of the liver and kidney are becoming more evident. Diversified physiologic activities require a corresponding variety of properly devised test methods. It is evident that the clinician must decide what specific function is to be measured, and the clinical pathologist must have a method of suitable specificity if reliance is to be placed on laboratory reports indicting the functioning ability of any organ.

The laboratory contribution to knowledge of the state of the kidneys comes, aside from the examination of the urine and blood, in the study of the following: 1. Ability of the kidneys to concentrate and dilute the urine. 2. Ability of the kidneys to eliminate foreign substances introduced into the body. 3. Ability of the kidneys to eliminate easily measured normal constituents of the blood (clearance tests).

There is no unanimity of opinion as to the best renal function test in present clinical usage.<sup>1-16</sup> The urea clearance procedure has had widespread application following the careful and extensive study of its use by Van Slyke and collaborators<sup>1, 17-20</sup> at the Rockefeller Institute. Van Slyke finds the urea clearance fairly immune to unpredictable extra-renal influences, especially disturbances in water metabolism. He also finds that a normal clearance does not necessarily prove the absence of renal disease, but states that he does not consider the performance of a multiplicity of tests necessary.<sup>18</sup> Alving and Van Slyke<sup>1</sup> warn that normal clearances are encountered in the presence of obvious renal abnormality in the following conditions: 1. Mild acute nephritis. 2. Recovery stage of acute nephritis. 3. Some cases of nephrosis. In recovery from acute nephritis a low specific gravity persists long after the clearance returns to normal.<sup>1, 6</sup> It was further found that in

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cases of essential hypertension and nephrosclerosis showing normal urea clearance the concentration tests are likely to be normal, i.e., the clearance and concentration tests show the same relative behavior.<sup>1</sup>

Dodds and Robertson<sup>21</sup> think that the urea clearance is perhaps the most valuable of all renal function tests, while in the hands of Chapman and Halsted<sup>2</sup> the fractional phenol red test is as informative as the urea clearance. Leiter<sup>6</sup> and McDonald<sup>22</sup> consider the urea clearance the most reliable single test in their experience with renal function measurements. Freyberg<sup>4</sup> finds, on good evidence, that the concentration test of Lashmet and Newburgh<sup>12, 23</sup> is the most sensitive test of renal efficiency, often demonstrating impairment of function when other tests fail to do so. Kestel<sup>10</sup> likes the concentration tests best of all. Thomas<sup>8</sup> prefers a quantitative metabolic study such as the Mosenthal test day meal.

In an attempt to clarify the issue McDonald<sup>5</sup> points out that in one instance the difficulty in excretion pertains to the nitrogenous metabolites, whereas in another the difficulty is in excretion of water and salts. He concludes, "it is hardly conceivable that any single ideal test for renal function, especially in the diseased kidney, can ever be attained." He looks upon an adequate concentration test as probably the most sensitive indicator of damaged renal function. Ellis and Weiss<sup>7</sup> stress the fact that alterations in the formation of urine may occur from disturbances of either the filtration or reabsorption activities of the kidney. They use the creatinine clearance of Rehberg as a "direct indication of the amount of glomerular filtration" and stress that, under conditions of maximal excretion, the urea clearance also gives a relative index of the degree of filtration since with urinary excretions exceeding two cubic centimeters per minute the percentage of back diffusion of urea through the tubules is nearly constant. For tubular function Ellis and Weiss<sup>7</sup> consider the concentration test the best measure of the ability of the kidney to reabsorb water and, hence, of tubular activity. In conclusion, the authors emphasize the increasingly obvious fact that "no single technical procedure is adequate to test thoroughly the function of the kidney . . . these laboratory methods are of value only in supplementing clinical observation. They supply worthwhile information only when conducted with care under controlled conditions and the results obtained require careful interpretation." Leiter<sup>6</sup> summarizes the factors in such a careful interpretation as follows: "It is evident that the information acquired in this manner is a resultant of several factors, namely, the degree of parenchymal integrity of the kidney, the volume of blood flowing through the organ during the period of the test, the activity of compensatory physiologic or anatomic changes, and the presence or absence of various extrarenal conditions. The net result is a quantitative value for kidney function at the moment. Nothing is learned which is responsible for the quantitative change. Nor does one know from renal function testing alone whether the change has occurred in the remote or recent past, whether it is still active, or whether it will subside in the near or distant future." Harding and Urquhart,<sup>24</sup> Van Slyke,<sup>19</sup>

and Bowen<sup>11</sup> have stressed the influence of factors other than functional activity of kidney units on the kidney function tests. McCance<sup>25</sup> has demonstrated that disturbances in plasma electrolytes, for example low chloride values, may result in high blood urea values with temporary impairment in renal function, in the absence of nephritis in the clinical sense.

The present investigation concerns the application of four commonly used clinical methods, namely, the early morning urine specific gravity after a 12 hour fast, the excretion of phenol red, the urea clearance, and a combined dilution and concentration test similar to those used by Volhard, Lundsgaard, Rosenberg and others.<sup>1</sup> Purposely, the usual clinical laboratory equipment was selected in place of refinements in apparatus which are not commonly used. This observance, together with the fact that we have no new or favorite renal function test to present, will, it is hoped, render the results fairly applicable to the average hospital laboratory.

The use of phenol red in the study of kidney function was introduced by Rowntree and Geraghty.<sup>26</sup> As Chapman and Halsted,<sup>2</sup> Shaw and McKenzie<sup>27</sup> found the elimination of phenol red in the first 15 minutes to be a more reliable indicator of renal function than other periods in fractional dye excretion studies, such a procedure was adopted for the present study. The history of the use of urea in measuring renal function has been described elsewhere.<sup>18</sup> Van Slyke accepts as normal anything below 23 mg. urea nitrogen per 100 cubic centimeters of blood. Only after the urea clearance is 20 per cent or less of normal does an elevated blood urea commonly occur.

The morning specific gravity observations were made on 77 individuals for controls. The other methods, described below, were applied to 100 patients showing no evidence of disease, for the purpose of establishing controls. A separate group of 290 patients were selected for study. Each patient in this group presented a history, physical findings, or urinary sediment indicating renal disease. In other words, in each patient of the experimental group there was definite reason to suspect some degree of impaired renal function before the function tests were applied. In the beginning an attempt was made to use the method of Lashmet and Newburgh<sup>12,28</sup> to obtain the maximum specific gravity. From the ward patients we heard undue complaining of thirst, frequent refusals to coöperate. Occasionally the patients obtained water surreptitiously. For such reasons the attempt to determine the *maximum* urine concentration routinely was abandoned. An indication of the concentrating ability was obtained (a) by noting the specific gravity of urine after withholding fluids for 12 hours, and (b) by noting the maximum change in specific gravity after taking a large volume of water (i.e., the lowest reading in the urine specific gravity following the ingestion of 1500 cubic centimeters of water in the morning subtracted from the highest reading in the afternoon). From our preliminary experience with the procedure of Lashmet and Newburgh<sup>12, 28</sup> we have reason to believe that it is superior to all methods for estimating maximum concentrating ability. Its drawback lay in the lack of coöperation from the

average ward patient with the hospital attendants in the effort to obtain adequate dehydration.

### METHODS

The methods employed were as follows: The patient received a standard "house diet" in the hospital for 48 hours prior to the tests. No fluids were allowed from seven o'clock in the evening until seven o'clock on the morning of the dilution and concentration tests. No breakfast was given. At seven o'clock in the morning a specimen was taken for routine urinalysis. Between seven and eight in the morning the patient drank 1500 cubic centimeters of tap water. Urine was collected at the following hours: 7:30, 8:00, 8:30, 9:00, 9:30, 10:00, 10:30, 11:00, 11:30, 12:00, 1:00, and 2:00. A dry lunch (containing nothing which could be poured) was allowed at 11:30 in the morning during the test. The volume was measured and the specific gravity of the various specimens was determined by means of a standardized clinical urinometer. A notation was made of the four hour volume excreted from 7:00 until 11:00 in the morning. The urine collected between 9:00 and 10:00 and between 10:00 and 11:00 o'clock was taken for determinations of the urine urea by the method of Koch.<sup>28</sup> Blood for urea estimation by the method of Koch was taken at 10:00 o'clock. From this the urea clearance was calculated by the formula of Van Slyke<sup>17, 18</sup> for maximum urea clearance. The patient remained in bed during the procedure outlined above. On a separate day (usually the day before or immediately after the above) 6 mg. of phenol red were given intravenously 30 minutes after the patient had taken 16 ounces of water. Urine was collected after 15 minutes and two hours. Each patient had a recorded history and physical examination with notes on clinical observations which might affect the measured function. Tabulations made from these charts include the following information: Name; age; sex; urinalysis, including microscopic findings on centrifuged specimens; phenol red excretion for 15 minutes and two hours with the volumes excreted; the largest and smallest volume and the highest, lowest, and early morning specific gravity readings of the urine (including the hour of each) after 1500 cubic centimeters of fluid; the four hour volume during the dilution test; the urea clearance in terms of percentage of normal; the diagnosis; blood pressure; and, in a miscellaneous column, facts in the history, physical examination, or laboratory reports of significance in each patient. Corrections for albumin in the urine were made according to Lashmet and Newburgh<sup>23</sup> for the specific gravity readings of urine ( $0.003 \times$  per cent of protein).

After plotting the results of tests on the control series one finds notable left skewing in the frequency distribution diagram for urea clearance, phenol red excretion and Volhard type concentration tests (charts 2, 3, and 4). The figures for early morning specific gravity are fairly symmetrically distributed and give a mean of 1.026 and a standard deviation of  $\pm 0.003$  (chart 1).



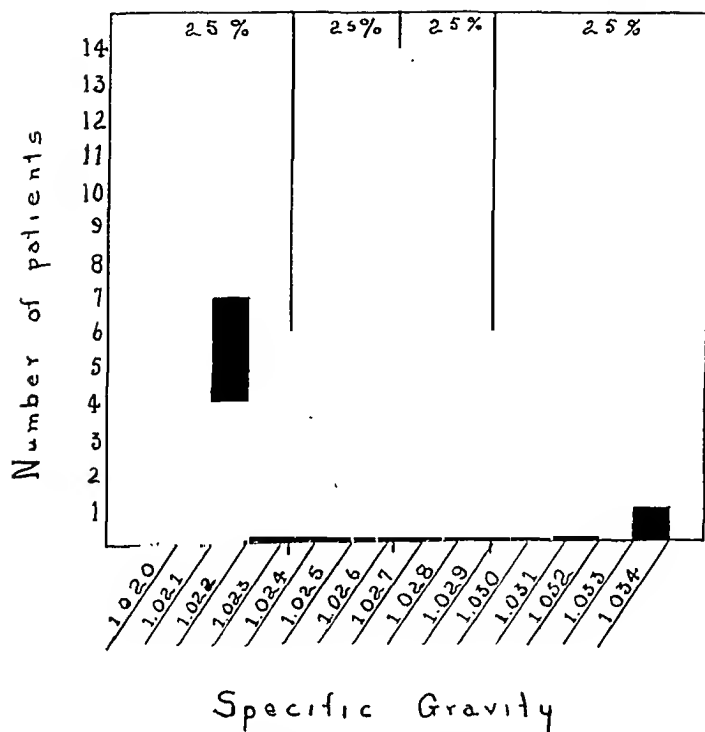


CHART 1. Distribution of morning specific gravities after 12 hour fast in normal adults.  
Mean 1.026, standard deviation 0.003.

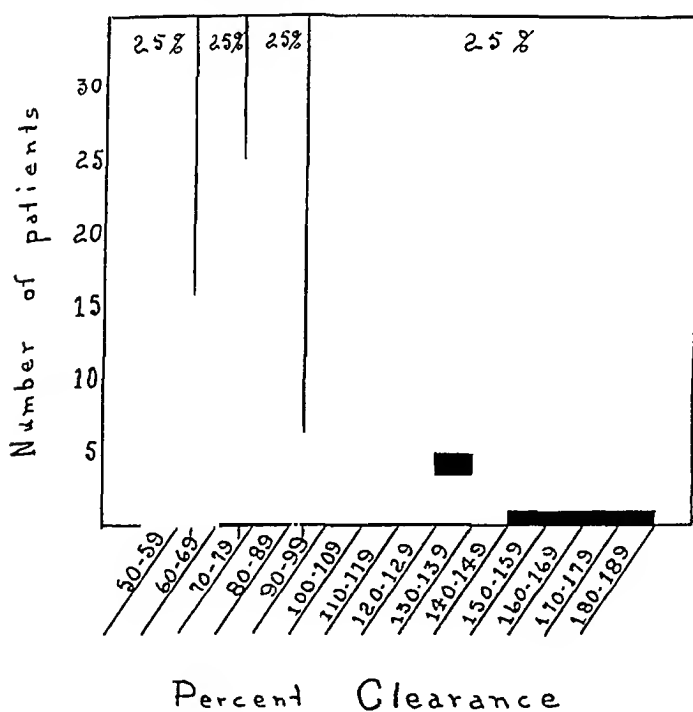


CHART 2. Distribution of maximum urea clearances in normal adults.

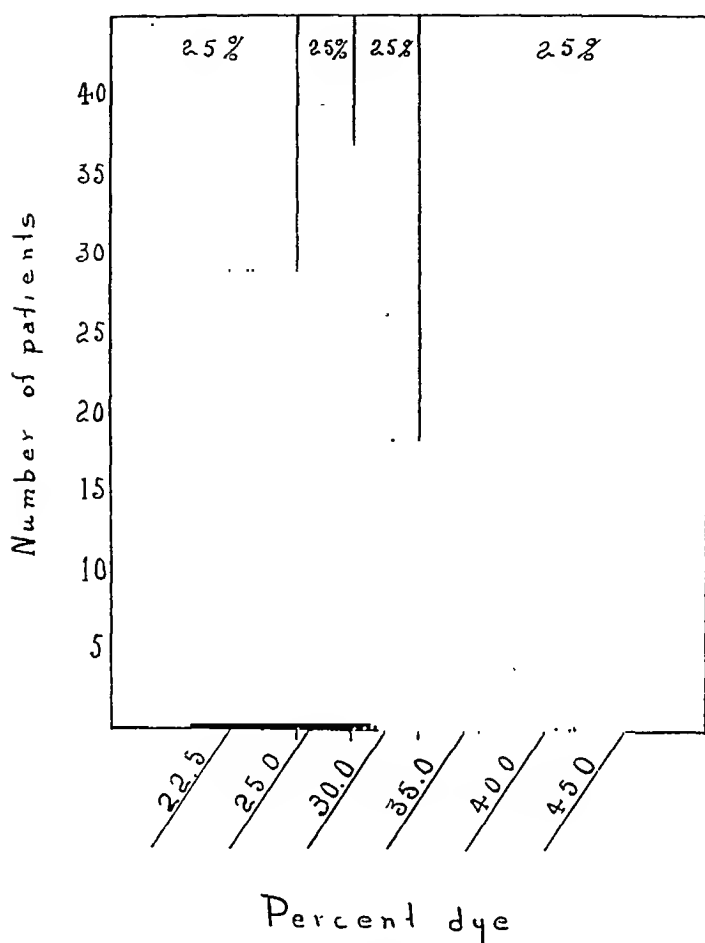


CHART 3. Distribution of phenol red excretions 15 minutes after intravenous injection of the dye in normal adults.

For purposes of interpretation of results in the diseased group of patients, urea clearance readings below 50 per cent (assuming 75 cubic centimeters of blood cleared per minute for maximum clearance in the normal) were regarded as showing evidence of renal disability. Excretion of less than 25 per cent phenol red in 15 minutes, a change in specific gravity during the Volhard type concentration test of less than 0.010, and a morning specific gravity of less than 1.020 was taken as evidence of inadequate function for the particular test.

The clinical diagnoses are shown in table 1. An effort was made to separate those patients with the suspected etiology of renal arteriosclerosis without hypertension from the group showing nephrosclerosis with hypertension. Hypertension was arbitrarily taken as a systolic pressure reading above 150 millimeters and diastolic reading above 92 in a reclining patient. For each group the number of instances in which the phenol red excretion, the concentration tests, and the urea clearance were found to be impaired is given. It is found from table 1 that the 15 minute phenol red excretion is more apt

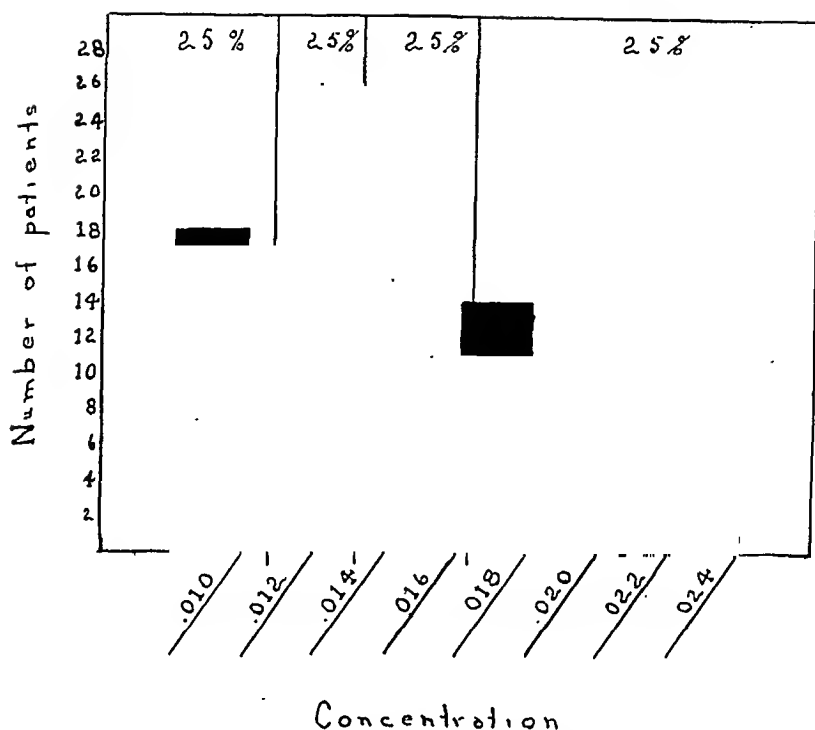


CHART 4. Distribution of degrees of variation in specific gravity obtained by subtracting lowest morning reading from highest afternoon reading. Vollhard-type concentration test in normal adults.

TABLE I

The Incidence of Impaired Function Tests in Relation to the Clinical Diagnoses

Diagnostic Class	Number Patients	Impaired PSP Excretion		Impaired Concentration		Impaired Urea Clearance	
		Number	%	Number	%	Number	%
Arteriosclerosis (without hypertension)	70	62	89	48	69	36	51
Arteriosclerosis (with hypertension, benign and malignant)	86	68	79	60	70	62	72
Hemorrhagic Bright's disease:							
(a) acute	16	12	75	4	25	6	38
(b) subacute	16	12	75	4	25	10	62
(c) chronic	26	24	92	22	85	24	92
Degenerative and toxic Bright's disease (including pyelonephritis, toxemias of pregnancy)	52	46	88	28	54	30	58
Congenital polycystic kidneys	2	2	100	2	100	2	100
Unclassified	22	16	73	10	45	16	73

to show evidence of disease in patients with arteriosclerosis and without hypertension than is the specific gravity or the urea clearance. This is likewise true for the patients with degenerative Bright's disease from various causes.

In only 94 of the group of 290 patients in whom renal disease was suspected, did all tests show evidence of impairment. Inasmuch as the results of the dilution test paralleled those of the concentrations in all but three instances, the former is omitted from separate consideration. Table 2 groups those patients, aside from the 94 having diminished function in all tests, with disease manifest by one or two of the procedures employed.

TABLE II  
Impaired Renal Function Indicated by but Two of the Test Methods

	Number of Patients
Phenol red plus urea clearance.....	56
Phenol red plus dilution and concentration.....	54
Dilution and concentration plus urea clearance.....	18
Impaired Renal Function Indicated by but One of the Test Methods	
	Number of Patients
Phenol red alone.....	32
Urea clearance alone.....	30
Dilution and concentration alone.....	6

### COMMENT

Laboratory procedures, to be helpful to the clinician, must have their advantages and limitations defined. The relative dependability or lack of specificity should be recognized by the successful clinical pathologist as well as the clinician. Otherwise, harmful misdirection in planning the patient's existence results not infrequently. Astuteness in interpretation of all evidence pertaining to a patient's illness is rendered more necessary than ever by the increasing multiplicity of laboratory aids. In the group of patients studied clinically and reported here, it is noted that only in the instances of advanced renal disease did all function tests agree. Each member of the group of 94 furnished sufficient evidence in the anamnesis, physical examination, and the urine sediment to assure a physician of the presence of moderately advanced disease without the confirmation of function tests. The group represents patients so advanced in their disease that little effective medical protection can be given.

It is highly important that early signs of disease be recognized. This applies to subacute or chronic hemorrhagic Bright's disease, the toxic and arteriosclerotic types as well. It is to the interest of the patient that renal tests indicate changes in the maximum functioning ability of that organ sufficiently early to allow steps to be taken to give some effective degree of

rest and protection before the stage of renal failure has been reached. The tests employed do not appear to meet this requirement satisfactorily. Don,<sup>3</sup> after comparing the function tests in 64 patients having impaired renal excretion observed that, "In making comparison one was struck by the fact that while on one occasion one test would seem to be the most sensitive, in another case it would seem to be the least sensitive. . . . The phenolsulphon-thalein is not regarded as a very sensitive test, yet in many cases, chiefly those with a high blood pressure, I found it to be apparently a delicate test and low results were obtained more often than I expected. It was still more surprising to find that it sometimes showed an apparent loss of renal function before the urea clearance test. . . . To conclude, the failure of the tests to agree closely with one another suggests either that they are not completely reliable or that different renal functions are being measured."

Under disadvantages described for the urea clearance are: 1. Accurate collection of urine for a given period is necessary.<sup>6</sup> 2. Exacting procedures are needed for the careful quantitative determinations of blood and urine urea.<sup>6</sup> 3. Penington<sup>20</sup> stated that the rate of urea excretion is increased by the administration of milk, caffeine and glutamic acid by mouth, decreased by exercise, pituitrin and large amounts of adrenalin. On the other hand, Page<sup>30</sup> found that diuretics, salyrgan, caffeine and diuretin do not alter the ability of the kidney to excrete urea. 4. Van Slyke<sup>19</sup> observed that extra-renal factors as changes in blood supply resulting from shock, reflex anuria after surgery, cardiac decompensation, interfere with the clearance. Obviously, similar objections may be made to other tests of renal function.

Concentration tests are commonly invalidated because of extra-renal influences of endocrine, nervous or metabolic origin.<sup>1, 6, 7</sup> Diuresis at the time of the test in an edematous patient makes impossible the carrying out of sufficient dehydration to obtain a sufficiently high specific gravity of the urine. When the diet of the patient has been low in protein and salt there may not be sufficient excretion of waste products in even small volumes of urine to grant a high specific gravity that should occur with normal renal function. A low specific gravity may be found in anemias, pyelitis, prostatic hypertrophy, urethral strictures, paralysis of the bladder. Low specific gravity is a regular finding in diabetes insipidus.

Disadvantages in the use of the phenol red test have likewise been described. Leiter<sup>6</sup> finds that cardiac failure has an unusually depressing effect on the elimination of phenol red by otherwise normal kidneys. A certain amount of dye is held by blood proteins. Increased absorption might well prevent an adequate test. Thomas<sup>8</sup> speaks of the uncertain fate of part of the phenol red in the body tissues, and finds that pregnancy interferes with its excretion. Freyberg, Gillard and Ganesbauer<sup>9</sup> find the 15 minute phenol red excretion unreliable in the last trimester of pregnancy. As is common knowledge, urinary pigments dilute the red color and give rise to uncertain matching of the dye. Collins<sup>31</sup> found a yellow color filter useful in the matching of phenol red with the standard solution. Of various sug-

gested procedures for removing bile pigments in urine<sup>32</sup> the use of aluminum hydroxide was found to be the most satisfactory in our laboratory. This is troublesome, and at times seems to give a false low reading for the dye present.

At times it was observed that even after adequate preparation of the patient the volume of urine excreted was low, or the patient could not void at the required minute. For the 15 minute determination of dye excretion it is essential that the patient void completely or be catheterized at the proper time. This means occasional repetition of the test. Twice the presence of hemolyzed blood in the voided specimen invalidated the reading. At other times the color of the diluted and alkalinized urine was of such a bizarre hue that matching was impossible. No explanation has been found for the latter behavior.

The dilution and concentration tests of the Volhard type are of no service in the patient who vomits easily from any cause. The test is nullified occasionally by the presence of duodenal obstruction or other gastrointestinal disease interfering with rapid absorption. It is found useless, of course, in the presence of edema, hepatic cirrhosis, hepatitis, or ascites.

A practical defect in the urea clearance estimation is discovered in occasional errors in the time of the collections of the urine by hospital attendants. Coöperation of the nursing service as well as that of the patient is required in getting the exact time of the voidings and insuring complete emptying of the bladder. In a few instances inordinately high urea clearances were obtained—200 per cent or more than normal. These are inexplicable in spite of careful checking of the calculations and the consistent use of duplicate determinations. In such patients a normal clearance figure may be found the following day. One wonders if such a peculiar clearance might not occur infrequently at a lower range and give a false normal reading in diseased kidneys.

At best it seems that the present laboratory estimations of renal function fall short of the clinical requirements. It is hoped that future efforts in function testing may be directed toward measurement of the specific separate functions of the kidney, keeping in view the anatomic basis for renal disease. The functional adequacy of the blood supply, the glomeruli, and the tubules may ultimately lend themselves to separate measurement. Progress is being made toward this ideal. The difficulties encountered in the approach to adequate and safe methods which will measure accurately for the clinician the separate functions of the kidney are clearly indicated in the review of knowledge of renal tubular excretion by Shannon.<sup>33</sup>

### CONCLUSIONS

It is obvious that no one test was adequate in the clinical study of these patients. The 15 minute excretion of phenol red gave expected results more often than any other measure employed. From this experience it appears that phenol red cannot be displaced by any available procedure in convenience

and accuracy for clinical use. When combined with the urea clearance determination, laboratory confirmation of renal disease was obtained in all but six of a group of 290 patients presenting good clinical or urinary sediment signs of renal disease.

*Note:* The authors are indebted to the nursing service of Davis Memorial Hospital for faithful coöperation, to Mr. C. L. Corder for loyal assistance in the required urinalyses.

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# CLINICAL STUDIES IN RENAL DISEASE. III. ACIDOSIS IN CHRONIC GLOMERULONEPHRITIS \*

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UREMIA is a toxic state associated with an abnormal accumulation of nitrogen bodies in the blood. It is characterized clinically by anorexia, nausea, vomiting, weakness, restlessness, headache, drowsiness or coma. The exact nature of the toxemia of uremia is not known, although such substances as urea, uric acid, creatinine, phosphates, sulphates are present in the blood in excessive amounts. It was Bright himself who first designated as uremia the group of symptoms characteristic of renal failure, because he thought these symptoms were due to a retention of urea in the blood. Bright regarded urea as a highly toxic substance but it is now generally acknowledged that he was mistaken, for in Bright's disease there may be a very high concentration of urea in the blood without symptoms of toxemia. It is to be stressed, however, that uremia is always associated with marked urea retention in the blood as well as in the tissues and the demonstration of this retention establishes the diagnosis.

The toxemia characteristic of the uremia resulting from Bright's disease is dependent upon many factors. Sepsis, malnutrition, dehydration, oliguria, cardiovascular insufficiency, respiratory complications and anemia, singly or collectively are obviously important. The presence of any one of these factors will not only aggravate the existing renal insufficiency but may lead to a fatal ending regardless of the degree of actual renal damage.

Knowledge of the exact mechanism of the symptoms of uremia is incomplete and the physiological cause of death is obscure. An important factor is acidosis which was first described in Bright's disease by Von Jaksch <sup>1</sup> in 1888 and subsequently confirmed by recent studies. This acidosis in nephritis has been discussed at length by Peters and Van Slyke <sup>2</sup> who report that in fatal cases of nephritis, extreme acidosis comparable to that seen in diabetes mellitus may exist and stress that in terminal nephritis acidosis "may attain a severity great enough in itself to menace life." The clinical importance of this fact has not been emphasized generally and with this in view the results of a study of the symptoms and the CO<sub>2</sub> combining power in a group of 50 cases of chronic nephritis are presented in this paper.

A diagnosis of chronic nephritis was made by the findings of hypertension, anemia, urea nitrogen of 50 mg. or more, a low fixed specific gravity, and red blood cells and casts in the urinary sediment. In all of our patients the nephritis had undoubtedly existed for many years. Symptoms of toxemia had been present for only a short time because the symptoms leading to admission to the hospital had existed for a period of less than 30 days.

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Acidosis (a  $\text{CO}_2$  combining power of 40 vol. per cent or less) was found in 36 patients (table 1). The symptoms of uremia were found to be not unlike those of acidosis of any cause (table 3). Acidosis, once developed, manifests the same symptoms whatever the factor responsible for its inception. It is of primary importance in chronic nephritis with uremia.

TABLE I  
Blood Chemistry  
Mg. per 100 c.c.

No.	Age	B.P.	$\text{CO}_2$ Vol. %	Cr.	Ca.	$\text{PO}_4$	Urea N	Days in Hosp.	S.S.*	R.†
1.	33	200/130	35.6	4.5	9.6	5.8	160	24	m.	I.
2.	49	190/110	12.6	9.0	—	—	160	34	S.	D.
3.	26	260/160	23.0	9.2	7.5	17.2	140	6	S.	D.
4.	59	200/140	24.0	12.0	9.2	9.4	250	11	S.	D.
5.	65	180/85	32.4	8.25	—	—	91	17	S.	I.
6.	31	195/110	35.0	4.0	9.5	4.4	110	21	S.	D.
7.	47	210/105	33.4	12.0	5.9	16.4	176	9	M.	I.
8.	60	110/60	29.6	5.0	—	—	115	4	S.	D.
9.	24	225/155	35.3	12.0	10.0	9.4	150	18	M.	D.
10.	34	212/130	13.7	4.0	6.5	6.5	60	5	S.	D.
11.	64	110/70	39.3	1.58	—	—	60	10	M.	I.
12.	52	168/90	13.6	8.0	7.0	12.4	130	28	S.	I.
13.	76	128/70	52.2	2.5	—	—	75	18	m.	I.
14.	60	220/100	60.7	2.67	—	—	80	10	m.	I.
15.	33	150/80	41.9	2.5	7.9	2.2	55	8	m.	I.
16.	28	210/140	23.6	8.4	6.8	23.6	100	12	S.	I.
17.	60	100/94	37.5	2.36	—	—	60	17	S.	I.
18.	51	160/90	37.6	3.7	7.0	8.0	73	12	m.	I.
19.	39	140/80	10.3	10.0	5.8	14.0	200	4	S.	D.
20.	24	210/170	26.5	8.0	6.8	11.6	125	14	S.	D.
21.	34	142/78	14.5	9.0	9.6	12.0	176	5	S.	D.
22.	33	54/0	41.0	1.67	8.7	7.2	74	7	m.	I.
23.	49	180/100	42.8	10.0	8.6	11.4	136	9	m.	I.
24.	60	60/60	47.0	6.0	—	—	140	10	m.	I.
25.	80	172/80	52.6	2.5	—	—	80	26	m.	I.
26.	47	140/68	33.8	12.0	—	—	220	12	S.	D.
27.	61	190/100	38.3	3.0	—	—	85	34	S.	I.
28.	30	270/175	32.0	2.0	12.2	6.4	55	42	m.	I.
29.	25	245/155	26.8	8.0	9.5	8.0	100	3	S.	D.
30.	54	195/100	23.0	8.5	5.5	18.0	140	2	S.	D.
31.	32	250/160	27.0	12.0	8.6	18.0	375	7	S.	D.
32.	34	160/90	53.0	4.2	—	5.6	150	26	m.	I.
33.	51	200/98	43.0	6.6	10.0	5.3	94	31	M.	I.
34.	29	200/160	45.0	12.0	10.6	16.5	220	23	M.	I.
35.	46	220/120	29.0	8.6	9.8	9.2	190	36	S.	I.
36.	70	230/100	46.0	2.0	7.4	4.5	192	7	M.	I.
37.	46	145/95	26.0	7.5	6.0	8.4	150	18	S.	D.
38.	67	130/80	48.6	2.5	—	—	60	12	m.	I.
39.	54	220/140	37.0	6.0	10.0	6.0	100	22	M.	I.
40.	60	225/110	38.0	3.7	9.5	4.4	85	7	M.	D.
41.	31	118/65	28.0	3.3	12.0	14.8	75	16	S.	I.
42.	28	120/70	42.0	20.0	6.4	17.6	340	25	M.	I.
43.	65	190/120	52.0	2.2	9.2	4.2	50	12	M.	I.
44.	47	250/180	17.0	10.0	7.0	16.8	200	5	S.	D.
45.	47	140/72	9.3	8.6	10.0	14.0	200	2	S.	D.
46.	43	180/90	24.0	7.0	8.6	16.0	150	7	S.	D.
47.	32	210/110	31.0	12.0	9.2	8.0	170	16	M.	D.
48.	49	190/110	32.0	6.0	10.0	9.0	80	11	S.	I.
49.	36	180/110	26.0	7.0	8.6	12.0	110	27	S.	I.
50.	41	178/120	18.0	9.0	9.5	10.0	120	4	S.	D.

\* S.S. severity of symptoms, m. mild, S. severe, M. moderate.

† R. result, I. improved, D. died.

TABLE II  
CO<sub>2</sub> Combining Power in Uremia

Vol. %	No. of Cases
77-53 .....	3
53-40 .....	11
40-30 .....	15
30-20 .....	13
20-15 .....	2
Below 15 .....	6

TABLE III  
Frequency and Duration of Symptoms of Uremia

Symptoms	Frequency in Chief Complaint	Duration
1. Weakness .....	40	22 days
2. Vomiting .....	38	5 "
3. Restlessness .....	34	9 "
4. Nausea and poor appetite .....	33	26 "
5. Nocturia .....	33	3 years
6. Drowsiness .....	30	3 days
7. Headache .....	30	68 "
8. Muscular twitching .....	29	7 "
9. Difficulty in breathing .....	27	17 "
10. Swelling of ankles .....	16	19 "
11. Blurred vision .....	11	34 "
12. Loss of weight .....	9	96 "
13. Convulsions .....	7	15 hours
14. Diarrhea .....	6	5 days
15. Itching .....	5	12 "
16. Coma .....	4	7 hours

Acidosis occurs in chronic nephritis because of retention of phosphates and sulphates and the inability of the kidney to elaborate ammonia so that the alkali reserve is depleted by the retained acid. The ultimate course of chronic nephritis leads to death, but at any one time, serious acidosis may exist out of proportion to the degree of structural renal changes. Life may be terminated prematurely, because of acidosis and not because of actual irreparable renal damage. The toxemia is the cause of death. The uremia is an index of renal inadequacy which need not be irreparable.

In table 1 it appears that the severity of the symptoms of advanced nephritis and uremia is directly proportional to the degree of acidosis and not always nor exactly to the extent of nitrogen retention. This table also illustrates the evidence that severe symptoms existed in all instances in which the CO<sub>2</sub> combining power was less than 35 vol. per cent regardless of the degree of nitrogen retention. The symptoms commonly ascribed to nitrogen retention (table 3) are not unlike those characteristic of acidosis from any cause. The majority of the symptoms causing disability were present for a period of less than 30 days prior to admission to the hospital (tables 4 and 5). A consideration of tables 6 and 7 suggests that decrease in CO<sub>2</sub> combining power indicates a greater degree of renal insufficiency than nitrogen

TABLE IV  
Uremia  
Symptoms Present Less than 30 Days

1. Itching . . . . .	12 days
2. Difficulty in breathing . . . . .	17 "
3. Swelling of ankles . . . . .	19 "
4. Weakness . . . . .	22 "
5. Nausea and poor appetite . . . . .	26 "

TABLE V  
Uremia  
Symptoms Present Less than 10 Days

1. Coma . . . . .	7 hours
2. Convulsions . . . . .	15 "
3. Drowsiness . . . . .	3 days
4. Diarrhea . . . . .	5 "
5. Vomiting . . . . .	5 "
6. Muscular twitching . . . . .	7 "
7. Restlessness . . . . .	9 "

retention. Tables 1, 6 and 7 show that in advanced nephritis a CO<sub>2</sub> combining power determination is a very valuable index of renal function. It has been found to be more important than the creatinine figure in arriving at a prognosis. The mortality and the duration of life were constantly proportional to the degree of acidosis but not always to the degree of creatinemia. The recognition of the occurrence of acidosis in advanced nephritis is of clinical importance because it offers a therapeutic aid, the use of which may enable the clinician to tide over a patient ordinarily considered hopelessly ill, alleviate serious symptoms or avoid a fatal ending in those cases in which

TABLE VI  
The Mortality of Acidosis in Chronic Nephritis

CO <sub>2</sub> Vol. %	Number of Cases	Number of Fatal Cases	Per Cent of Fatal Cases	Days in Hospital
35-25	15	7	46.6	13
25-15	7	6	85.0	5.6
Below 15	6	6	100.0	4.6

TABLE VII  
The Mortality of Creatinemia in Chronic Nephritis

Creatinine Mg. per 100 c.c.	Number of Cases	Number of Fatal Cases	Per Cent of Fatal Cases	Days in Hospital
2-5	19	4	21.0	9.2
5-10	22	13	60.0	6.0
Above 10	8	5	62.0	10.0

renal function may be temporarily but not permanently exhausted. Case reports 2 and 12 illustrate this point.

With a creatinine of 8 and 9 mg. per cent respectively in these cases, one ordinarily would be justified in estimating a life expectancy of two or three

## CASE 2

M. C., female, 49 years of age, admitted to L. I. C. H., December 20, 1933.

*Chief Complaint:* Restlessness, weakness, heavy breathing, stupor and coma.

*Blood Pressure:* Systolic 190, diastolic 110; urine: sp. gr. 1.008–1.010, heavy trace of albumin, casts and red blood cells present.

*Blood Count:* Hemoglobin 68 per cent (Sahli); red blood cells 3,460,000.

<i>Blood Chemistry:</i>	date 12/20	12/25	12/30	2/20
Urea nitrogen, mg. per 100 c.c.	160	140	120	60
Uric acid, mg. per 100 c.c.	7	9.6	7	5.0
Creatinine, mg. per 100 c.c.	9	7.2	10	4.6
Calcium, mg. per 100 c.c.	9.2	—	8	
Phosphorus, mg. per 100 c.c.	13.4	—	7.2	
CO <sub>2</sub> (Vol. %)	12.6	40	37.0	44.0

*Clinical Diagnosis:* Uremia; chronic glomerular nephritis.

*Treatment:* 300 c.c. 4 per cent sodium bicarbonate intravenously every 12 hours 6 doses; every 24 hours 2 doses; sodium bicarbonate by rectum and later by mouth 60 gr. three times daily.

*Result:* Chief complaint relieved in 36 to 48 hours, and patient continued free of symptoms except for weakness. She survived for 15 months.

## CASE 12

R. P., female, 52 years of age, admitted to L. I. C. H., October 22, 1934.

*Chief Complaint:* Nausea, vomiting, restlessness, muscular twitchings and stupor.

*Blood Pressure:* Systolic 168, diastolic 90; urine: sp. gr. 1.005–1.011, albumin measurable quantity, casts and red blood cells present.

*Blood Count:* Hemoglobin 53 per cent (Sahli); red blood cells 3,100,000.

<i>Blood Chemistry:</i>	date 9/25	9/28	10/18	10/22
Urea nitrogen, mg. per 100 c.c.	130	120	75	100
Uric acid, mg. per 100 c.c.	6.6	5.9	6	4.6
Creatinine, mg. per 100 c.c.	8.0	6.7	6	5.0
Calcium, mg. per 100 c.c.	7.0	—	8.0	
Phosphorus, mg. per 100 c.c.	12.4	—	6.2	
CO <sub>2</sub> (Vol. %)	13.6	29.0	40.3	41.4

*Clinical Diagnosis:* Uremia, chronic glomerular nephritis.

*Treatment:* 250 to 300 c.c. 4 per cent sodium bicarbonate intravenously repeated as indicated by CO<sub>2</sub> combining power every 12 hours.

*Result:* Stupor relieved in 24 hours. Balance of chief complaint relieved in 5 days. The patient is still living after 2½ years.

months in either instance—but following the correction of the acidosis, the patient described in Case 2 lived 15 months and the one in Case 12 is still alive at the end of two and a half years. In both instances the nitrogen retention diminished with the correction of the acidosis, although in other cases there has been a striking improvement in symptoms but none in the nitrogen retention.

Case 12 illustrates the disappearance of toxic symptoms after relief of the acidosis even though the nitrogen retention persisted.

Case 2 shows a decline in the nitrogen retention after relief of the acidosis.

This phase of the value of correcting the acidosis found in chronic nephritis has been presented in a recent paper.<sup>3</sup> It is of interest here to mention that convulsions did not occur in any of the fatal cases in which the acidosis was corrected, and that one patient lived for six months with an extensive pericarditis, complicating uremia.

In chronic nephritis structural, progressive and irreparable changes are so often present in the kidneys that the term cure cannot be legitimately applied. It may, however, be used for the relief of severe symptoms, such as vomiting, restlessness, drowsiness, which may in some cases constitute the only complaint, or coma, which if unrelieved leads to death.

The existing acidosis, if allowed to remain, not only produces serious symptoms but it deprives the uremic patient of any chance of recovery. If a cure is not possible, relief of symptoms and prolongation of life in such an exceptionally serious condition as uremia are important and valuable.

### CONCLUSIONS

1. Severe acidosis is a frequent finding in cases of uremia.
2. The symptoms of toxemia in uremia are similar to the symptoms of severe acidosis from other causes.
3. In cases of uremia without severe acidosis subjective symptoms are mild.
4. In cases of uremia a  $\text{CO}_2$  combining power determination is important and serves as a valuable prognostic aid.
5. In cases of uremia the greater the acidosis the shorter is the duration of life.
6. A  $\text{CO}_2$  combining power determination in advanced nephritis is a valuable test of renal function.

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# THE AZORUBIN S TEST OF LIVER FUNCTION; AN EVALUATION, WITH A COMPARATIVE STUDY OF THE BROMSULPHALEIN AND HIPPURIC ACID TESTS \*

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FEW tests of liver function have proved to be of much value in the diagnosis and prognosis of diseases of this organ. Common to all is the failure to detect hepatic disease in its earlier stages. The multiplicity of the liver's functions, as well as its great regenerative capacity and functional reserve, provides ample explanation for this shortcoming. Although a better understanding of the condition of the liver may be derived from a combined study of several hepatic functions, any test which might elicit more trustworthy information concerning a single function deserves further investigation.

Azorubin S,† a dark red, stable, water soluble dyestuff of the mono-azo group, was first introduced as a test of hepatic function by Tada and Nakashima<sup>19</sup> in 1924. They injected it intravenously and, by duodenal intubation, observed the color changes in the bile. In normal subjects as much as 95 per cent of the dye was excreted in the bile, the remainder being eliminated in the urine. Thus, renal disturbances can exert only a negligible influence upon its excretion by the liver. A delay in appearance of dye in the bile, or a prolonged urinary excretion, was regarded as of pathologic significance. It was found to be harmless and devoid of untoward effects, and when compared with 62 other dyes, yielded more reliable results (bromsulphalein was not included in their study).

Fenstermann (1926)<sup>2</sup> observed a close parallelism between the extent of liver damage and the impairment in the hepatic excretion of azorubin S. Studying patients with "catarrhal jaundice," atrophic cirrhosis and cholecystitis, Lebedow (1930)<sup>5</sup> found the test a very useful and reliable index of liver function. When the clinical manifestations of catarrhal jaundice were maximal no dye was eliminated in the bile, whereas the urine remained deeply colored for as long as 24 hours. Regression of the syndrome was marked by the reappearance of biliary dye. Cirrhosis uniformly manifested a delayed hepatic excretion. Nakashima (1934)<sup>7</sup> noted several instances of liver disease in which the dye excretion was accelerated, and suggested that this response might be due to a "compensatory hyperfunction"

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† The Azorubin S solution used in this study was prepared by George A. Breon & Co., Kansas City, Missouri.

of the liver. Weiss (1935),<sup>21</sup> in his studies, found azorubin S preferable to bromsulphalein. More recently, Eppinger (1937)<sup>2</sup> corroborated the findings of the earlier investigators and extolled the virtue of the azorubin S test. He considered it of greatest value in the differentiation of "catarrhal" from parenchymatous jaundice, the presence of bile-stained duodenal contents in the absence of biliary dye indicating the latter form. In some cases of suspected liver damage without icterus the azorubin S test was unique in its detection of impaired function.

Such enthusiastic reports merit further confirmation and study. We have, therefore, performed the azorubin S test on 14 normal subjects and on 27 patients with hepatic disease. The results in the latter group are compared with those of the bromsulphalein test, generally regarded as the most satisfactory test of the excretory function in patients without clinical jaundice; and with those of the hippuric acid test, which determines the detoxifying function of the liver, and is reported to be reasonably accurate in the diagnosis and prognosis of disease in individuals with manifest jaundice.<sup>16</sup>

## METHODS

*Azorubin S Test.* After an overnight fast, a narrow flexible tube is passed into the duodenum and its position confirmed fluoroscopically. When bile begins to flow through the tube, 4 c.c. of a sterile 1 per cent aqueous solution of azorubin S are injected intravenously. Five minutes later, 40 c.c. of 25 per cent aqueous magnesium sulfate solution are administered through the duodenal tube. The duodenal contents are collected in separate test tubes at one to two minute intervals, and the time elapsing between the injection of the dye and the appearance of a very deep red efflux is designated as the "appearance time." For color determinations and comparisons the best results are obtained by observing the solutions in bright daylight; slanting the tube against a white background is also helpful.

Using a colorimetric method, Zinny (1926)<sup>23</sup> measured the amount of dye excreted in the bile, and found that an excretion of less than 0.01 gm. in one hour is significant of liver damage. Although perhaps more accurate, this method seemed unnecessary. Fenstermann<sup>3</sup> preferred a simple colorimetric examination of the urinary dye, but this procedure proved unreliable in our hands.

*Hippuric Acid Test.* The technic was that originally described by Quick,<sup>10</sup> "method 1" being used for the quantitative analyses. In accordance with the modification of Kohlstaedt and Helmer,<sup>4</sup> the hourly specimens of urine were pooled and a single determination made. An excretion of 3 gm. of hippuric acid, in terms of benzoic acid, was considered normal, with 85–115 per cent of this value as the normal range.<sup>10</sup>

*Bromsulphalein Test.* The method was similar to that described by Rosenthal and White,<sup>14</sup> except that the amount of dye injected intravenously



was calculated on the basis of 5 mg. per kilogram of body weight.<sup>8, 12</sup> A single sample of blood was drawn 30 minutes after administration of the dye. From our observations on normal subjects, a retention of more than 10 per cent may be regarded as abnormal.

In all cases the tests were performed on successive days, in order that the results might be comparable.

## RESULTS

*Normal Subjects.* In normal individuals Tada and Nakashima<sup>19</sup> observed a very deep red discoloration of the bile 17 to 18 minutes after injection of azorubin S. Fenstermann<sup>3</sup> found the range of normal to be 15 to 30 minutes, while Eppinger<sup>2</sup> considered it to be 15 to 20 minutes. In their study on arthritis Rawls, Weiss and Collins<sup>11</sup> accepted 15 to 30 minutes as the normal range.

In order to become familiar with the normal limits of variation, as well as to define them more precisely, the azorubin S test was performed on 14 normal subjects. Usually a succession of color changes in the bile was noted in the following order: orange, reddish-orange, light red, light cherry red and deep cherry red, after which the color faded out in the reverse order. The appearance time of the significant test color (deep cherry red) ranged from 17 to 29½ minutes, whereas the first appearance of dye, however faint, varied from eight to 25 minutes (table 1). In three individuals, a burgundy wine color followed the deep cherry red and was observed 22½, 26½ and 27 minutes, respectively, after injection of the dye. In three subjects (numbers 4, 8 and 12) very dark brown bile (B bile) appeared after injecting magnesium sulfate. This, when stained by the dye, resembled a burgundy wine hue; but within five to seven minutes the bile became lighter

TABLE I  
Results of the Azorubin S Test in Normal Subjects

Subject	First Appearance of Biliary Dye (Minutes)	Appearance Time of Deep Cherry Red Bile (Minutes)	Comment
J. M.	10	19	
B. D.	16½	23½	
B. F.	8	18	
S. B.	20	29½	
D. V.	25	26	
G. M.	23½	29	
P. B.	15	17	
O. M.	15	20	
M. P.	17	27	
J. G.	16	29	
N. S.	13½	20½	Burgundy red—22½
F. M.	13	24	Burgundy red—27
J. B.	21	26	
W. L.	20½	24	Burgundy red—26½

in color and an accurate reading could easily be made. This incident was not encountered in any of our abnormal cases.

From the foregoing observations, and in agreement with the standard accepted by Rawls, Weiss and Collins,<sup>11</sup> the normal appearance time of a deep cherry red color was regarded as 15 to 30 minutes.

*Hepatic Cirrhosis.* Nineteen patients with cirrhosis were studied (table 2). Of these, 18 were in the hypertrophic stage and one was in the atrophic stage. The edge of the liver in the hypertrophic group extended 6 to 10 cm. below the costal margin in the mid-clavicular line on deep inspiration; the consistency was increased and the surface was smooth in all but three instances (numbers 1, 5 and 8). The spleen was palpable in 15 cases, and in the majority was only slightly enlarged. No patients with ascites were chosen for this study, for it was our intention to select individuals presenting less advanced grades of cirrhosis without portal decompensation. It was realized, of course, even in the absence of the latter phenomenon,

TABLE II

Comparative Results of the Azorubin S, Bromsulphalein and Hippuric Acid Tests

Pa- tient	Diagnosis	Azo- rubin S Appear- ance Time (Min.)	Brom- sulph- alein Reten- tion %	Hippuric Acid Excretion		Icterus Index	A/G	Comment
				Benzoic Acid Gm.	Excre- tion %			
1	Syphilitic cirrhosis	60	40	2.12	71	5	$\frac{3.95}{2.65}$	N.P.N. 38 P.S.P. Test—17%
2	Hypertrophic cirrhosis	∞ (41)	40	2.78	93	12	—	Cholesterol esters 112 Cholesterol total 252
3	Hypertrophic cirrhosis	∞ (54)	90	1.46	49	55	$\frac{2.9}{3.4}$	N.P.N. 24 Cholesterol total 320 Cholesterol ester 98 Macrocytic anemia
4	Hypertrophic cirrhosis	46	20-	3.29	110	9	—	N.P.N. 27
5	Hypertrophic cirrhosis (biopsy)	∞ (90)	70	—	—	22	$\frac{2.8}{4.7}$	Phosphatase 23 units Cholesterol total 154 Cholesterol esters 38 Macrocytic anemia
6	1. Hypertrophic cirrhosis 2. Cholelithiasis	41	40	3.46	115	5	—	Cholesterol total 166 Cholesterol esters 62 N.P.N. 41 Cholesterol and calcium bili- rubinate crystals in bile
7	Hypertrophic cirrhosis	∞ (71)	20	—	—	20	—	Phosphatase 16 units
8	Hypertrophic cirrhosis (biopsy)	∞ (60)	30	2.42	81	13	—	N.P.N. 27 Cholesterol total 210 Cholesterol esters 93
9	Hypertrophic cirrhosis	51	40	3.14	105	10	—	N.P.N. 31
10	Hypertrophic cirrhosis	35	10	3.44	115	6	—	N.P.N. 31 Cholesterol total 189
11	Hypertrophic cirrhosis	36	20+	2.90	97	11	—	N.P.N. 30
12	Hypertrophic cirrhosis	45	30	1.59	53	6	—	N.P.N. 40
13	Hypertrophic cirrhosis	42	20+	3.10	103	7	—	Urea N 17

TABLE II—*Continued*

Patient	Diagnosis	Azo-rubin S Appearance Time (Min.)	Brom-sulph-alein Retention %	Hippuric Acid Excretion		Icterus Index	A/G	Comment
				Benzoic Acid Gm.	Excretion %			
14	Hypertrophic cirrhosis	∞ (54)	60 <sup>a</sup>	3.13	104	8	—	N.P.N. 30
15	Hypertrophic cirrhosis	∞ (45)	50	1.14	38	12	—	N.P.N. 29 Cholesterol total 145 Cholesterol esters 36
16	Hypertrophic cirrhosis	33	50	3.80	127	—	—	N.P.N. 25
17	Hypertrophic cirrhosis	∞ (60)	100	2.89	96	15	$\frac{4.0}{2.25}$	N.P.N. 26
18	Hypertrophic cirrhosis	37	70	2.62	87	5	$\frac{5.15}{3.05}$	N.P.N. 35
19	Atrophic cirrhosis	∞ (52)	90	1.12	37	22	$\frac{1.83}{3.27}$	N.P.N. 38 Cholesterol total 208 Cholesterol esters 113 Macrocytic anemia
20	Chronic hepatitis	33½	5	3.39	113	9	—	N.P.N. 29
21	Chronic hepatitis	∞ (70)	10	3.46	115	5	—	N.P.N. 33
22	Chronic hepatitis	∞ (64)	5	2.99	100	—	—	N.P.N. 29
23	1. Chronic hepatitis 2. Cholelithiasis	37	20	4.01	134	5	—	N.P.N. 26 Cholesterol and calcium bilirubinate crystals in bile
24	Subsiding acute hepatitis	26½	20	—	—	22	—	Van den Bergh—direct and indirect immediate positive
25	Acute toxic hepatitis	34	50	2.33	78	24	—	N.P.N. 34
26	Acute toxic hepatitis	∞ (45)	100	3.13	104	36	—	N.P.N. 29
27	1. Fatty metamorphosis of liver 2. Diabetes mellitus	35	20	1.48	49	5	—	N.P.N. 38 Cholesterol total 176

∞—indicates that the biliary drainage never became deeper than an orange red or pale red color. The length of the observation period following dye injection is shown in parentheses. P.S.P.—Per cent phenolsulphonephthalein excretion in 1 hour (intravenous method).

that the disease, strictly speaking, is usually not in an early stage by the time the clinical diagnosis has become unequivocal.

The azorubin S test was positive in all 19 patients, the appearance time being definitely delayed in each case (table 2). In nine instances, the bile never acquired more than a reddish orange or pale red color. Serum albumin and globulin determinations made on five of these nine patients revealed a reversal of the A/G ratio in four, thus indicating a more advanced stage of hepatic disease. Indeed, those individuals presenting a harder, larger or more diffusely involved liver, generally, though not invariably, manifested a greater delay in hepatic excretion. Three of the four patients with a lowered serum albumin fraction also exhibited a macrocytic anemia. The urine, which normally is discolored for three to 11 hours after injection of the dye,<sup>10, 3, 5</sup> and which, in hepatic disease, has been observed to remain colored for proportionately longer periods, was of no value as an indirect measure of liver damage in the three patients studied in this manner. In

patient 1, the dye never appeared in the urine; in patient 23, it had disappeared within four hours; and in patient 2, within six hours.

The bromsulphalein test was positive in 18 out of the 19 patients, comparing exceedingly well with the azorubin S test. Excluding the single bromsulphalein failure, a case of Banti's syndrome, the azorubin S test was more strongly positive than the bromsulphalein in two patients (numbers 4 and 7), whereas in two others (numbers 16 and 18) the converse held true. In general, however, the bromsulphalein retention in this group paralleled the delay in azorubin S excretion.

The hippuric acid test, performed on 17 patients, proved disappointing. Positive results were obtained in only six instances, and in these bromsulphalein and azorubin S tests were strongly positive. In the remaining 11 individuals, negative to the hippuric test, the azorubin S test was uniformly positive, whereas the bromsulphalein test was positive in 10.

*Other Forms of Hepatic Disease.* Under this heading are included two cases of acute toxic hepatitis, one of subsiding acute hepatitis, one biopsy-proved case of marked fatty metamorphosis of the liver associated with diabetes mellitus, and four cases of relatively early, mild chronic hepatitis.

The azorubin S and bromsulphalein tests were positive in the two patients with toxic hepatitis, whereas the hippuric acid test was negative in one of these. In the patient with subsiding acute hepatitis, the bromsulphalein test was positive and the azorubin S test negative, but the significance of the bromsulphalein response is difficult to evaluate, since unreliable results are often obtained with this dye in cases of jaundice, particularly if the Van den Bergh reaction is direct.<sup>18</sup> All three tests were positive in the individual with fatty metamorphosis of the liver.

The four patients with chronic hepatitis are noteworthy from a diagnostic and therapeutic standpoint. They had been observed by able clinicians prior to these studies, yet, as not infrequently happens in these cases, the possibility of an hepatic disorder apparently had received little if any consideration. The histories being suggestive of biliary tract disease, cholecystograms and roentgenographic studies of the gastrointestinal tract had been made. In three patients normal findings had been reported and the symptoms ascribed to a "functional" disorder. In the fourth patient (number 23) cholelithiasis was suspected but could not be substantiated during the earlier period of observation. All 4 patients presented a slightly enlarged liver of somewhat increased consistency, which was tender on moderate pressure and on fist percussion; in two of them the spleen was just palpable on inspiration. We strongly suspected liver disease (chronic hepatitis), but the diagnosis needed corroboration. Significantly, the azorubin S test was positive in all four instances. The bromsulphalein test was positive in only one, and the hippuric acid test was uniformly negative. In accord with our diagnosis of hepatic disease and the results of the azorubin S test, a dietary regimen high in carbohydrate and low in fat was instituted.

The rapid subjective and objective improvement which ensued was most gratifying. The following summarized case history is illustrative:

*Case 22.* M. L., a white female, aged 33, was seen on April 29, 1937, complaining of heaviness in the epigastrium, bloating and belching of five and one-half years' duration. A recent diagnostic study done elsewhere (including blood count, Wassermann and Kahn, urinalysis, stool examinations, Ewald test meal, cholecystogram, gastrointestinal roentgenograms and basal metabolism) revealed no abnormalities. A diagnosis of "nervous disorder" had been made. Bland diet and sedatives were ineffective. The liver edge descended 6 cm. below the costal margin on deep inspiration, was tender on pressure, and of slightly increased consistency. Spleen descended 1 cm. below the costal margin on inspiration. On May 3, the azorubin S test was positive (first discoloration at 31 minutes; maximum intensity—light red at 44 minutes; progressively lighter thereafter). May 4, bromsulphalein test: 5 per cent retention at one-half hour. May 5, hippuric acid test: 2.99 gm. in terms of benzoic acid. Diagnosis: chronic hepatitis. Treatment: high carbohydrate, low fat diet. Within four days subjective improvement was first noted; 10 days later symptoms were "practically absent." Hepatic tenderness subsided rapidly. On January 29, 1938 the liver edge descended 1 to 2 cm. below the costal margin on deep inspiration.

*The Azorubin S Test Combined with a Crystallographic Study of the Bile.* Piersol, Bockus and Shay,<sup>9</sup> Shay and Riegel<sup>15</sup> and others have demonstrated the value of a microscopic study of bile in the diagnosis of cholelithiasis, indicating its superiority over the roentgenogram. They pointed out that the presence of both cholesterol and calcium bilirubinate crystals is pathognomonic, whereas the finding of only one of these elements is strongly in favor of gall stone disease. These observations have been confirmed by Bloch and Rosenberg.<sup>1</sup> Lyon<sup>6</sup> and others have also emphasized the value of a cytologic study of bile in the diagnosis of cholecystic disease. The technic of the azorubin S test lends itself to a combined study of liver function and composition of the bile. For the latter purpose the bile collected before and after injection of magnesium sulfate, prior to the appearance of the dye, may be utilized. In the present study we have searched for crystals in the bile in selected cases.

The coexistence of cholelithiasis with hepatic cirrhosis is not uncommon, the reported incidence being as high as 13 per cent.<sup>13</sup> Upper abdominal pain may be the predominating symptom in either disease, yet the finding of a non-visualizing gall-bladder cholecystographically may be of no diagnostic significance in the presence of cirrhosis, often leading to erroneous conclusions. In these cases the establishment of the presence of calculi, which is important therapeutically, may be impossible without a crystallographic study of the bile. The advantage of a combined liver function test and bile examination is illustrated by the following case abstract:

*Case 6.* M. P., a white male, aged 64, married, was seen on June 22, 1937, complaining of nausea, mild and severe attacks of epigastric and right hypochondriac pain, progressive loss of weight (15 kg.), weakness and constipation of three years' duration. Examination revealed a well developed, poorly nourished male. The liver edge was 10 cm. below the costal margin on inspiration, sharp, tender, and of increased consistency. Spleen: edge smooth, rounded, of increased consistency, and

6 cm. below the costal margin on inspiration. Blood count normal. Ewald test meal: free HCl, 29, total acidity, 56. Gastrointestinal tract normal roentgenographically. Three cholecystograms revealed no visualization of the gall-bladder. A diagnosis of hepatic cirrhosis was made. Cholelithiasis was suspected but could not be proved. December 20—Bromsulphalein test: 40 per cent retention in 30 minutes. December 21—azorubin S test: positive (appearance time—41 minutes). The bile, collected following magnesium sulfate instillation, was centrifuged for 20 minutes. Microscopically the sediment showed large numbers of cholesterol and calcium bilirubinate crystals, denoting calculi. Accordingly, a high carbohydrate regimen followed by cholecystectomy was recommended, but the latter was refused by the patient.

In this instance the technic of the azorubin S test, as utilized by us, served a dual purpose: first, that of measuring the function of the liver, and second, that of disclosing evidence of calculi.

The importance of a preoperative study of liver function in cases of cholelithiasis and cholecystitis is now generally appreciated. That the combined method under consideration may be useful in recognizing latent forms of hepatic insufficiency, and in detecting or corroborating the presence of calculi, is shown by the following case abstract:

*Case 23.* I. R., a white female, aged 63, was seen on June 2, 1937, complaining of nausea, heartburn, belching, bloating, epigastric pain and constipation of "many" years' duration. Examination revealed a well developed, well nourished woman. The liver edge was 5 cm. below the costal margin in the mid-clavicular line on deep inspiration, sharp, of increased consistency and tender on pressure. Spleen: edge just palpable on inspiration. Histamine fractional gastric analysis: free HCl, 0; total acidity, 10. Roentgenographic studies of the gastrointestinal tract showed multiple diverticula of the colon and hypermotility of the sigmoid. Cholecystogram: Normal except for a questionable translucent area in the gall-bladder shadow. Bromsulphalein test: 20 per cent retention in 30 minutes. Azorubin S test: positive (appearance time, 37 minutes). Microscopic examination of the bile sediment revealed many cholesterol and calcium bilirubinate crystals. In the light of these findings, a diagnosis of cholelithiasis with chronic hepatitis was made. The cholecystogram was then repeated and showed positive evidence of at least two gall stones. The indications for medical management, directed toward the hepatitis, followed by cholecystectomy were thus clearly evident.

#### COMMENT

The value of the bromsulphalein test in recognizing widespread or moderately advanced liver disease has already been established. Hence, its close agreement with the results of the azorubin S test in our patients with cirrhosis and acute hepatitis, particularly the former, may be regarded as confirmatory evidence of the reliability of the azorubin S test in such conditions. Moreover, the detection of lesser degrees of hepatic insufficiency (chronic hepatitis) by the azorubin S test, in the face of bromsulphalein failures (three out of four cases), is significant and concurs with the experience of Eppinger.<sup>2</sup> However, in view of the small number of such cases studied, our results are suggestive but not conclusive as to the superiority of the azorubin S test. In accord with the observations of Fenstermann,<sup>3</sup> a rough parallelism between the delay in hepatic excretion of azorubin S and

the degree of liver damage is discernible in our series. In none was the dye excreted more rapidly than normal. Further, the urinary excretion of azorubin S as an indirect test of liver function, originally proposed by Tada and Nakashima<sup>19</sup> and extended by Fenstermann<sup>3</sup> and Lebedow,<sup>5</sup> is untrustworthy as shown by Eppinger<sup>2</sup> and early in our work.

The added merit of a liver function test which permits simultaneous microscopic study of the bile should not be underestimated. As exemplified by patients 6 and 23, the technic of the azorubin S test is well adapted for this procedure, and may prove valuable in cases of cholelithiasis both from a medical and a surgical point of view.

The discordant results obtained with the hippuric acid test, as compared with those obtained with the other tests, were most surprising. Of 24 cases thus studied, 17 of which were cirrhosis, 15 were negative. Comparing the hippuric acid and bromsulphalein tests in three patients with decompensated portal cirrhosis and in three individuals with obstructive jaundice, Snell and Plunkett<sup>17</sup> found the former test positive in five and the latter positive in all six. Vaccaro<sup>20</sup> considered the hippuric acid test "more accurate" than bromsulphalein, but little reliance can be placed on this phase of his investigation, because of the small number of comparable cases studied with the bromsulphalein test, the lack of uniformity in the technic of the latter as employed in different patients, and because his range of normal values for hippuric acid excretion is now regarded as too narrow. From a review of the literature,<sup>4, 10, 17, 20, 22</sup> it is apparent that a large proportion of the reported cases of cirrhosis studied with the hippuric acid test presented a far advanced stage of the disease. There was either a reversal of the albumin-globulin ratio or portal decompensation, or both. This may explain the discrepancy between former reports and our own. If this explanation is correct, the usefulness of the hippuric acid test is restricted to patients with the more advanced grades of chronic disease without adequate hepatic regeneration, or to those with more acute, diffuse damage, either initial or in a state of exacerbation. Our findings would seem to indicate that the integrity of the detoxifying function of the liver remains intact longer than has been hitherto appreciated.

Finally, like many other tests, the azorubin S test has certain disadvantages. The obvious practical objection is that duodenal intubation may be time consuming and should be accompanied by fluoroscopic observation of the tube in situ. It is also essential that the examiner become well acquainted with the normal for the proper interpretation of this test in the abnormal. Nevertheless, should the test prove as useful as the trend of our results indicates, its disadvantages would be far outweighed by its advantages.

### SUMMARY

1. The azorubin S test of liver function, which has received little attention in this country, was performed on 14 normal subjects; and a compara-

tive study of this test with the bromsulphalein and hippuric acid tests was made in 19 cases of cirrhosis, two cases of acute toxic hepatitis, one case of subsiding acute hepatitis, one case of fatty metamorphosis of the liver and four cases of relatively early chronic hepatitis.

2. The azorubin S test was found to be as reliable as the bromsulphalein test and better than the hippuric acid test in cases of cirrhosis.

3. In the cases of relatively early chronic hepatitis, the azorubin S test was superior to both the other tests.

4. Although the azorubin S test requires duodenal intubation, the method lends itself to a simultaneous crystallographic study of the bile. Illustrative cases are cited in which the combined technic was used to advantage.

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# THE PROBLEM OF RHEUMATISM AND ARTHRITIS

## REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1938

(Sixth Rheumatism Review)\*

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## Part I

## GENERAL INCIDENCE OF RHEUMATIC DISEASES; SOCIAL AND ECONOMIC IMPORTANCE

IN our preceding Review<sup>5</sup> were given preliminary data from the National Health Survey indicating that "rheumatism" was by far the most common chronic disease in the United States, and ranked second in producing both temporary and permanent disability. Further data from this survey have appeared.<sup>970-975</sup> Conducted by the United States Public Health Service, the survey involved a house-to-house canvass of about 800,000 families comprising about 2,800,000 persons in 83 cities and 23 rural areas of 19 states. Among 2,152,741 white persons questioned were 11,997 whose sole or primary cause of disability was rheumatism: of these, 592 were under 15 years of age, 560 were aged 15 to 24 years, 7,953 were aged 25 to 64 years, and 2,892 were older. Over 50 per cent (6,358 persons) were from poor families: 3,079 were on relief, 3,279 were members of families whose annual income was under \$1000.00.<sup>975</sup>

The incidence of "rheumatism and allied diseases" on a given day in the United States was estimated to be about one (0.099 per cent) per 1000 persons.<sup>972</sup> The incidence per 1000 persons according to age and sex was as follows: less than 0.05 for persons under 15 years of age; 0.9 among those aged 15 to 64 years, and 5.4 for those aged 65 years or more. The incidence per 1000 females of all ages was twice that for males. It was 1.2 for females of all ages, negligible for those under 15 years of age, 1.1 for those aged 15 to 64 years, and 6.6 for those older. The incidence per 1000 males was 0.6 for those of all ages, negligible for those under 15 years, 0.6 for those aged 15 to 64 years, and 3.8 for those older.<sup>972</sup>

Applying these figures to the total population it was estimated that there were 6,850,000 cases of rheumatism in the United States in 1937, or more than the *total number* of all cases of heart disease, cancer and other tumors, tuberculosis and diabetes. Rheumatism caused an annual loss from work of 97,200,000 days, and produced 147,600 permanent invalids. The mortality from rheumatism was 3.4 per 100,000 persons<sup>973</sup> and among chronic diseases rheumatism ranked fourteenth as a cause of death.

[It is difficult to compare these statistics with those noted in previous Reviews. In 1933 the Massachusetts survey indicated an incidence of 3,264,000 persons with chronic rheumatism in the United States. In 1936 Kling<sup>4</sup> estimated that there were 2,700,000 patients with chronic rheumatic diseases in the country. In this National Health Survey rheumatism was broadly defined and included "rheumatism, arthritis, gout, neuralgia, neuritis, lumbago, acute rheumatic fever, stiff neck and other muscular pains."<sup>975</sup> For various reasons the survey has been subjected to considerable criticism.<sup>110, 977</sup> The field work was done by about 7000 canvassers drawn from the relief rolls of the Works Progress Administration and included former salesmen, nurses, teachers, social workers and so forth. All were given at least a week of preliminary intensive training for their work. In 350,000 instances the diagnoses were confirmed by later inquiries from attending physicians.<sup>970</sup> Even so it is difficult to believe that the diagnoses of rheumatism were accurate. Differentiation of the rheumatic diseases is difficult enough for physicians and well nigh impossible for laymen. Hence some critics<sup>110</sup> have discounted the accuracy of this "doorbell survey conducted by W. P. A. laymen." In the present state of our knowledge of the rheumatic diseases no survey would be any too accurate even if canvassers were physicians. But at least these figures indicate again that the rheumatic diseases are very prevalent in the United States.—Ed.]

A few new statistics were reported from other countries. Davidson and Rae stated that in 1936 there were among the insured population of

Scotland (35 to 40 per cent of the total population) "no fewer than 50,000 cases" of rheumatism in its various forms which caused the huge total of 3,500,000 days' incapacity. This entails an annual economic loss of two or three million pounds. It was estimated that in Scotland 334,872 new cases of rheumatism develop annually.

From the statistics of the National Health Insurance Society of Ireland O'Reilly attempted to make the first survey on the incidence of rheumatism in that country. Among an insured population of 500,000 persons were 16,000 who claimed disability because of rheumatism during 1935. Rheumatism was responsible for the greatest number of claims, the largest amount of money paid out in claims (131,000 pounds) and the greatest amount of incapacity (295,000 weeks in the year) of all diseases in Ireland.

According to Finn there are great numbers of cases of chronic rheumatism or arthritis in South Africa, probably as many as in other countries whose statistics have been reported. This gives further evidence that this disease-group is a world wide scourge. The influence of industry, occupation and housing on the incidence of the rheumatic diseases in various countries was discussed in detail (Conybeare and Glover; Fox; Van Bree-men). Exposure to cold and to occupational fatigue were considered to be more important factors than others, e.g., humidity.

#### DEFINITION OF RHEUMATISM; CONTENT OF "THE RHEUMATIC DISEASES"

"Rheumatism" and the rheumatic diseases have never been adequately defined. Current literature does not clarify the terms. The origin of the term "rheumatism" and the history of the various forms of "chronic rheumatism" were outlined by Rolleston in a scholarly paper which will serve as an excellent source of original references and will especially interest those concerned with the genealogy of the rheumatic diseases. The relationship of the various rheumatic diseases to one another was discussed by Poynton,<sup>72</sup> and the French concept of "arthritisme" was defined by Bezançon and Weil. According to Fox<sup>328</sup> chronic rheumatism includes separate but allied diseases the earliest common feature of which is a characteristic abnormality in the patients' reactions to changes in external environment, especially to cold. Since there is no known common pathologic lesion to identify rheumatic disease, the authors of this Review will, as previously, use the layman's broad anatomic concept of rheumatism and will discuss herein a wide variety of diseases of joints and related structures.

#### CLASSIFICATION OF DISEASES OF JOINTS AND RELATED STRUCTURES

Recently few writers have indulged in new classifications of the rheumatic diseases. Ellman discussed the merits and demerits of several classifications. The year's literature presented a few minor revisions of older classifications not important enough for extended comment here.

Among them was O'Connor's classification based on the assumption

that the three basic etiologic factors in arthritis are bacteria, toxins and trauma. A first group "infectious arthritis" was separated into two subdivisions (a) "bacterial arthritis"; use of this term was restricted to forms in which there is actual intra-articular invasion of identifiable bacteria, and (b) "toxic (infectious) arthritis" presumably due to a variety of bacterial poisons. A second group "non-infectious toxic arthritis" included those presumed to arise from (a) endogenous toxins ("intestinal or glandular dysfunction") and (b) exogenous toxins from food, medicines, biologic materials or industrial poisons.

[This classification possesses the same merits and demerits as those of other etiologic classifications, chief objection being that no *identifiable* toxins from bacteria or from "intestinal or glandular dysfunction" have ever been isolated and proved to be the cause of any form of human arthritis.—Ed.]

#### RELATIVE FREQUENCY OF THE RHEUMATIC DISEASES

Published data on the relative incidence of the rheumatic diseases vary greatly depending on the writer's practice, whether he is a general practitioner, or a physician supervising a clinic for ambulatory rheumatism patients or a spa. According to Davidson's estimate the 334,872 new cases of rheumatism developing in Scotland annually include 26,030 cases (7.7 per cent) of rheumatic fever, 20,284 cases (6.1 per cent) of rheumatoid arthritis, 31,382 cases (9.4 per cent) of osteo-arthritis, and 251,176 cases (76.8 per cent) of muscular rheumatism. The order of frequency of rheumatic and allied conditions among the insured Scottish population of Aberdeen and Kincardine counties was as follows (Rae): lumbago 810 cases, rheumatism (undefined) 724, muscular rheumatism 682, synovitis and bursitis 368, sciatica 221, arthritis (unspecified) 185, "subacute and [acute?] articular rheumatism" 93, "muscular (non-rheumatic)" 88, "chronic joint changes" 65, rheumatoid arthritis 25, osteo-arthritis 18 and brachial neuritis 16, a total of 3295 cases among 126,633 insured persons.

[Because of the vague diagnoses these statistics are not very useful except to indicate that nonarticular rheumatism was much more frequent in that locality than arthritis. Either the incidence of rheumatoid and osteo-arthritis was surprisingly low or criteria for its recognition were poorly understood. And do Scots no longer have gout?—Ed.]

Having treated about 5000 cases of rheumatism O'Reilly concluded that in any 100 cases of rheumatism 48 patients will have fibrositis, 32 rheumatoid arthritis, 13 osteo-arthritis, 5 gout and 2 ankylosing spondylitis.

[This ratio differs somewhat from that of one of us (P. S. H., 1935) who estimated that among 100 "rheumatism patients" seen in general office or clinic practice 30 to 40 would have atrophic (rheumatoid) arthritis, 25 to 30 hypertrophic (osteo-) arthritis, at least 10 to 20 fibrositis of various types, 7 to 10 traumatic (including static or "micro-traumatic") arthritis, 3 to 5 gouty arthritis, 3 to 5 miscellaneous types (arthritis with psoriasis, tuberculosis, ulcerative colitis, syringomyelia, etc.), 2 gonorrheal arthritis and rheumatic fever. In the arthritis clinic of the Presbyterian

Hospital, New York, the relative percentages are approximately as follows: hypertrophic arthritis 30, atrophic arthritis 25, nonarticular rheumatism 20, traumatic and postural arthritis 10, rheumatic fever 5, gonococcal arthritis 3, gout 1, miscellaneous 6 (M. H. D.). In general hospital practice the proportion of cases of rheumatic fever is usually higher than in general office or clinic practice.—Ed.]

### DISEASES OF JOINTS RELATED PRIMARILY TO TRAUMA

*Sprains and Strains.* Various types of sprains and strains, and methods for their diagnosis and treatment were reviewed.<sup>285</sup> To understand the mechanism for the production of sprains one must remember that there are three types of articular ligaments: (1) those which consist of simple thickenings of capsule, which thickenings are too indefinite to be defined by dissection (e.g., internal lateral ligaments of knees and ankles; indeed most articular ligaments); (2) extracapsular bands which, when dissected, stand out as isolated structures (e.g., external lateral ligament of knees; middle and posterior fasciculi of external lateral ligament of ankle); (3) intra-articular bands (e.g., crucial ligaments of knees; ligamentum teres of hips; intra-articular fibrocartilage of sternoclavicular joints).

Ligaments of type 1 rarely rupture completely unless subjected to forces sufficient to produce articular dislocation. When such ligaments are sprained, lesions generally occur at bony attachments, and no articular instability or hypermobility results. For such sprains Elmslie recommended the use of firm elastic pressure to prevent or reduce effusions, rest of the part for 24 hours, then application of adhesive bandages and use of the part; after seven days the adhesive strapping is removed, then massage and active, and if necessary, assistive movements are used. A sprain-fracture occurs when a portion of bone at the ligamentous attachment is pulled off. It may occur especially in fingers and at the femoral attachment of the internal lateral ligament of the knee. A variety of the latter is the Pellegrini-Stieda disease. When sprain-fractures affect fingers or toes, the part should be securely strapped; limited motion is allowed but massage avoided. Only after six or more weeks when swelling and tenderness have subsided should the strapping be removed and motion begun. For knees so affected compression bandages, gentle exercises and faradic stimulation were recommended.

[The time for healing varies with the severity of the injury. Children's ligaments heal rapidly.—Ed.]

When ligaments of types 2 and 3 are strained sufficiently to be ruptured, articular instability may result. When conservative measures (application of splints or plaster with the joint in a position to relax the affected ligament, and other measures) fail, surgical procedures to repair the ligaments are indicated.

*Internal and Other Derangements of Knee Joints.* Knee joints are most commonly affected by injury. Several papers reviewed the anatomic relationships of the knee joint and the differentiation of the common types of

internal derangement.<sup>75, 178, 469, 470, 563, 660, 754, 778</sup> The common internal derangements and associated lesions of knee joints were listed as follows: (1) injuries (displacement or fractures) of the internal or external semilunar cartilages (menisci), (2) fractures of tibial spine, (3) fractures of tibial tuberosity, (4) strains or ruptures of crucial ligaments, (5) strains or ruptures of lateral ligaments, (6) damage to the retropatellar fat pad, (7) loose bodies in the knee joint which generally result either from osteochondritis dissecans, osteochondromatosis or synovial enchondromata, (8) patellar fracture, (9) slipping patella (not truly an internal derangement but a condition which may occur with mild knock knees and may produce locking). According to Chatterton the conditions numbered 1, 2, 3, 6, 7 and 9 are likely to cause locking, the others (numbers 4, 5 and 8) are not. To the above list of internal derangements, most of which are produced by acute trauma, the Penns added several nontraumatic internal derangements. Bennett described in detail two unusual derangements: a large cyst of the subpatellar fat pad and a large fibrochondroma of the subpatellar fat pad.

Anatomic studies on the relative importance of the cruciate and collateral ligaments in maintaining the stability of knee joints were made by Horwitz and Davidson.<sup>469, 470</sup> They confirmed the opinion of others that the lateral ligaments, especially the internal, are chiefly responsible for preserving the intrinsic stability of the extended knee, and that the cruciate ligaments are of secondary importance and are not indispensable to stability of knee joints. Hence after articular trauma, the integrity of a knee is not markedly altered if cruciate ligaments alone are torn or excised, provided collateral ligaments remain intact. Thus, articular stability can be restored simply by repairing the injury to collateral ligaments and disregarding the cruciate ligaments. Mauck's operation for repairing collateral ligaments was recommended and described.

Various methods for the surgical and nonsurgical treatment of internal derangements were reviewed.<sup>75, 178, 563, 754, 778</sup> The joint should be given a chance to heal without surgical interference. If symptoms persist, or disappear only to return repeatedly, then only should surgical intervention be considered. Trivial lesions of articular cartilage produce no permanent disability. [But over a period of years they may predispose to or induce degenerative changes.—Ed.] After severe injury pieces of cartilage may be torn loose and remain viable for long periods as intra-articular loose bodies which generally must be removed. Damaged intra-articular fat pads may also have to be removed. Intra-articular fractures generally heal, but injury to synovial membrane may result in synovial thickening and villous formation. [It is the belief of one of us, A. J. K., that after trauma the synovial membrane heals promptly. Thickening and villous formation are due to arthritis caused by damage to articular cartilage which does not heal, and disorganization of the joint resulting from the healing of bone with incongruity of articular surfaces.—Ed.] Since semilunar fibrocartilages of knees possess no blood vessels except at their junction

with the coronary ligaments, these cartilages when injured do not repair satisfactorily, and their surgical correction is generally necessary.<sup>178, 563</sup>

Frequent locking of knees provides a special hazard for city dwellers which has often led to minor and major injuries, even to skull fractures; hence the condition should be corrected fairly early.

*Tennis Elbow.* This subject was well reviewed by Higgs, North, and West. The condition may affect tennis players and those in other sports or at certain occupations which involve forcible extension and supination of the elbow combined with a clenched hand. It rarely affects persons under 30 to 35 years of age. Symptoms were described in our First Review.<sup>1</sup>

The typical pain is felt in the region of the external epicondyle of the humerus and extends down the back of the forearm to the wrist. It is produced by movements involving sudden contraction of the radial extensors, and can be reproduced by Mill's test which consists in putting fingers and wrist in full flexion and pronation, and then extending the elbow. There is tenderness over or near the anterior aspect of the external epicondyle. When the patient pronates his forearm and extends his wrist to grasp even some light object, sudden weakness may cause him to drop it. Objectively the elbow appears normal, and when it is moved passively pain and stiffness are absent. No abnormality is indicated in roentgenograms.

The major factor is trauma. Symptoms may begin rather promptly but generally appear slowly a few days after acute direct or indirect injury. Marked differences of opinion exist as to the pathologic basis. Carp<sup>1</sup> and Cyriax<sup>3</sup> collected 26 different views thereon. With the majority of writers West considered the condition to be caused by tearing of the tendon of the extensor origin from the external epicondyle with resulting periostitis. Higgs concluded that secondary infection, perhaps from infected foci, is present in damaged tissue. Perhaps the condition represents a variety of separate entities.

Conservative treatment was recommended<sup>441, 713</sup> for early acute cases: rest, heat, the arm in a sling or immobilized in a suitable splint. Massage and motion make the condition worse. Many patients recover spontaneously. If the condition becomes chronic most patients can be cured, according to West and North, by one manipulation under anesthesia after the method of Mills (1928): full flexion of the wrist with full pronation of the forearm, the elbow then being brought into full extension. West found the method of Cyriax<sup>3</sup> generally unsuccessful. If manipulation is not accepted, the application of a cock-up splint for a month may be required. Strapping gives tardy relief; prolonged rest of the part is not acceptable to most victims. Higgs favored the frequent use of a surgical procedure which North considered rarely necessary, one to be reserved for the most stubborn cases.

*"The Obstetrical Shoulder."* During delivery the shoulder joints of infants are subjected to considerable obstetrical trauma which may produce simple distortion, fracture of a clavicle or, more often, an epiphyseal separation of the upper end of the humerus. Scaglietti described the successive clinical and roentgenologic features in 53 cases of the last condition, which



may produce a characteristic rigidity of the shoulder joint with lateral displacement and retroversion of the epiphysis.

*Treatment of Traumatic Arthritis: General Considerations.* To hasten return of articular function in cases of traumatic arthritis, and to prevent as much residual disability and posttraumatic neurosis as possible, the application of physical therapy should not be left solely to the patient, but should be supervised carefully by physicians or technicians skilled in its use.<sup>551</sup> Simple methods of home physical therapy should be supplemented by suitable forms of professional physical therapy and occupational therapy. The special advantages of hydrotherapy in cases of traumatic arthritis were again stressed (Copeman). Lasher was disappointed in the effects of heat on many posttraumatic articular effusions. Measurements of articular effusions two or three hours after local application of heat often indicated slight increases, rather than reductions, in articular size. Hence he favored early aspiration of effusions. Truslow described a simplified compression bandage for traumatized joints with or without effusion. One layer of an Ace bandage is applied, e.g., to the knee. Then two pieces of sponge rubber, each about 8 inches long and  $2\frac{1}{2}$  inches wide with a small crescent cut out to fit the sides of the patella, are placed one on each side of the patella. The application of the Ace bandage is then continued until the rubber is entirely enclosed. Tarsy advocated more frequent use of periarticular and intra-articular injections of local anesthetics to relieve pain in traumatic and other types of arthritis. Aqueous solutions of 1 or 2 per cent procaine hydrochloride were generally used. Intra-articular injections were sometimes superior to periarticular injections. Eucupine in oil was sometimes used periarticularly, but produced severe reactions when given intra-articularly. Although the duration of induced anesthesia was short, rather permanent relief was often noted.

[By such injections satisfactory results are not infrequently obtained in various types of arthritis.—Ed.]

A novel procedure was advocated by Waugh as a result of his studies on the pH of synovial fluid: the pH of normal synovial fluid is about 7.4, similar to that of blood. The pH of 20 traumatic effusions averaged 5.65 at 24 hours, 5.95 at 48 hours, 6.55 on the third day, and 7.7 on the seventh day after injury; in other words such effusions were acid for three days and then became alkaline. The acidity was thought to be due partly to the presence of lactic acid derived perhaps from local tissue—cell damage and degeneration. According to Waugh (1936) during the healing of a fracture the pH of the primary hematoma also becomes acid. Waugh reasoned that perhaps the acidity of such effusions is a physiologic response to trauma designed to excite local leukocytosis, mesoblastic proliferation and repair. Waugh attempted to imitate this reaction by treating 11 cases of traumatic and 5 cases of atrophic arthritis with intracapsular injections of a solution of procaine acidified to pH 5 with lactic acid. The formula of the solu-

tion (Bayer) to produce such an acidity was: novocaine—HCl 2.0 gm., NaCl 0.5 gm., N/5 lactic acid 0.2 c.c., water to 100 c.c. Amounts of the solution used were 2 c.c. for elbows and ankles, 4 c.c. for knees and shoulders. Patients were hospitalized for injections; the solution was injected "around as well as into the capsule" under strict asepsis, then the joint was moved to its full range in all directions, and the limb was immobilized in plaster for two weeks followed by the use of an Elastoplast support until function was regained. Although the 11 cases of traumatic arthritis so treated were "those of severe disablement which had resisted various forms of treatment" full functional recovery resulted in all.

[This work is very interesting but needs confirmation. Perhaps results were due, not to the injections, but to the measures used thereafter. Studies should be made on controls similarly treated except for the injections.—Ed.]

Synovectomy was performed by Inge in nine cases of "chronic proliferative synovitis traceable to chronic trauma, such as torn menisci or loose bodies." In all cases symptomatic and functional improvement resulted. Noting that Speed (1924) advocated synovectomy for traumatic arthritis, Swett stated: "It is gratifying to observe that complete recovery has been the rule in all of these cases thus far reported." He considered it logical to expect recovery after removal of chronically inflamed synovial tissue which has largely lost its function. Without reporting results of his own Swett concluded: "It may be confidently said that chronic traumatic arthritis provides one of the major indications for synovectomy."

[We believe that in general there should be a long minimal time limit to allow spontaneous healing before synovectomy. But under certain circumstances synovectomy may be indicated. In traumatic arthritis thickened synovia is the result not the cause of the trouble. If the underlying cause can be corrected surgically, then the thickened synovia can be removed at the same time with benefit, but if incongruity of articular surfaces is not corrected synovectomy cannot be expected to result in a permanent cure.—Ed.]

#### GONORRHEAL ARTHRITIS AND GONORRHEAL "RHEUMATISM"

*Incidence.* Despite efforts of national and civic bodies there is as yet no significant reduction in the incidence of gonorrhea in the United States. Reviewing the epidemiology of the disease, Vonderlehr and Usilton published the annual incidence of attacks of acute gonorrhea among white and negro males and females in 46 surveyed localities in the United States. The incidence per 1000 population varied from a maximum of 46.6 white males (Charleston, W. Va.), 69.9 negro males (Lincoln, Neb.), 15.1 white females (El Dorado, Ark.), and 46.5 negro females (Newton, Kan.) to a minimum of 2.3 white males (also Newton, Kan.), 6.6 negro males (Texarkana, Ark.), 0.2 white females (rural Nebraska), and 2.2 negro females (Omaha, Neb.). The European incidence of the disease also has not been reduced significantly (Fessler). The disease is not incurable, but the careless, inadequate attitude of the public, including patients and physicians, has so far been largely incurable.

[The incidence of gonorrheal arthritis was accepted<sup>139</sup> as being from 2 to 3 per cent of patients with gonorrhea. This incidence seems high to one of us (M. H. D.).—Ed.]

The patient's occupation may largely determine the site of his gonorrheal arthritis (Rorke). Most commonly affected are hands and wrists among manual workers, knees, feet or ankles among those who stand or walk a lot—waitresses, clerks, salesmen. Rorke concluded that severity of climate was also a factor in the incidence.

*Clinical Data.* Among 58 cases of gonorrheal arthritis seen by Burbacker and Weiland the ratio of monarthrititis to polyarthrititis was about 2:3. The site of involvement in order of frequency was knee, metatarsus, ankle, metacarpus, wrist, hip, elbow, sacro-iliac, shoulder, sternoclavicular and temporomandibular articulation. Infections of the knee constituted 44 per cent of the total joints affected.

Recent reports have emphasized the frequency and diagnostic significance of certain skin manifestations which may accompany gonorrhea and gonorrheal arthritis. According to Buscke (1912) gonococcal eruptions are of four main types: (1) erythemas, (2) urticarial and nodose lesions, (3) hemorrhagic and bullous lesions, (4) hyperkeratosis. Lesions recently described in cases of gonorrheal arthritis were erythema nodosum,<sup>4</sup> petechiae and small red sore spots associated sometimes with a central white necrotic area, at other times with vesiculation and seropurulent fluid.<sup>5</sup> Showers of petechiae, some with white centers, appeared in Lichtman's fatal case of gonococcal endocarditis with jaundice; no pelvic focus was found. Keil reported five cases of gonorrheal arthritis, gonococcemia and distinctive hemorrhagic vesiculopustular and bullous skin lesions. Although a history of old gonorrhea was generally obtained, in none of the five cases was an active local gonococcal focus found. Because the acute febrile polyarthrititis sometimes followed acute sore throat and especially since cardiac murmurs were present in two cases, diagnoses of rheumatic fever were entertained. However, gonococci were isolated (by smears, cultures or both) from blood, joints or skin lesions. [The fact that a sore throat or a respiratory infection often precedes acute gonorrheal arthritis has been noted by Schottmüller, 1921, Wheeler and Cornell, 1930, and Keefer and Spink, 1937.—Ed.] The five patients were young adults, profoundly ill, with a somewhat remittent but very irregular, atypical fever. In four cases gonococcal complement fixation tests on blood gave negative results; perhaps the method used was not sensitive enough. Despite the presence of cardiac (soft systolic apical) murmurs and the proved bacteremia, gonococcal endocarditis was apparently absent, as the murmurs disappeared and the patients recovered. The metastatic dermatosis present was "distinctive" and presumably caused by a hematogenous dissemination of gonococci rather than by toxemia. The typical eruption generally appeared during the febrile period, and tended to occur in crops; sometimes only one crop appeared. Generally only a few (1 to 8) lesions were present; occasionally they were distributed over the entire body.

They were usually discrete, rarely coalescent. They generally affected extremities, occasionally trunk, face, scalp. They appeared first as erythematous macules which speedily acquired a central vesicle or pustule. Hemorrhages typically occurred in the center of the lesion; often the exudation of fluid and cells caused bullous formation. "The classical lesion in full development is a hemorrhagic, purulent vesicle or bulla, surrounded by a more or less broad erythematous areola." The hemorrhagic feature may be absent. Keil discussed the differentiation of these lesions from the "rheumatic" and other dermatoses.

[Three of us (W. B., M. H. D., and P. S. H.) have recently seen four cases with similar skin lesions and with gonorrheal arthritis proved by articular culture; diagnoses were at first difficult because no active local lesion was found. Those concerned with diseases of joints should familiarize themselves with this skin lesion. In such cases efforts should be made to confirm the diagnosis by making cultures from the skin lesions and from blood.—Ed.]

Difficulties which may arise in diagnosing gonorrheal arthritis were illustrated in the cases of Reitzel and Kohl: in 14 of 25 cases of proved gonorrheal arthritis the history did not indicate previous gonococcic infection and either routine smears were "negative" or no urethral or cervical discharge was present. Diagnoses were made by recovering gonococci from blood (7 cases), synovial fluid (16 cases) or both (2 cases). Four patients had gonorrheal arthritis, gonococcemia and cutaneous eruptions such as those noted by Keil. Five patients had gonococcemia, arthritis and gonococcic endocarditis, the last being confirmed at necropsy in three cases. In one case of endocarditis a maculopapular eruption later became pustular, leaving necrotic centers and bullae from which gonococci were recovered. This contradicts the view of Keil that such eruptions do not occur in cases of gonococcal endocarditis.

[In our four cases of this skin lesion endocarditis did not develop.—Ed.]

*Pathology: Roentgenograms.* No new studies thereon were reported.

*Laboratory Data: 1. Identification of Gonococci in Smears.* Only an approved Gram-stain technic should be used to identify gonococci in "spreads" (smears).<sup>535</sup> The use of methylene blue and other short-cut stains leads to frequent errors. Gonococci may be particularly difficult to identify in smears from patients who have already taken sulfanilamide. In such cases the technic must be very exact.

*2. Cultures of Gonococci.* Accumulating evidence indicates that gonococci can be recovered by culture in about twice as many cases as by smears. Ch'ın obtained positive cultures from urine as often as from prostatic or urethral discharges. Since gonococci are viable in urinary sediment for 20 to 43 hours specimens could be sent fairly long distances for culture. New culture methods were proposed. Beck described a new chocolate agar; beef blood was used. A higher percentage of positive results and excellent growths of even weakly growing strains were obtained. For collecting material for cultures Greene and Breazeale advocated the use of swabs impregnated with sterile ascitic fluid. Reitzel and Kohl used hormone-brain broth or a brain-heart infusion with sterile ascitic fluid for culturing gonococci. The use of 8 per cent carbon dioxide did not seem essential to the successful recovery of gonococci.

3. *Gonococcal Complement Fixation Test.* This test was first used by Muller and Oppenheim (1902) as an aid in differentiating gonorrheal arthritis from other arthritides. Many physicians regard the test very highly: others consider it of limited value because of difficulties in its performance and interpretation. Results of the test are influenced by several factors as noted in previous Reviews and as again discussed by several authors.<sup>52, 490, 775, 1016</sup> From their studies on 760 patients Jacoby, Wishengrad and Koopman concluded that the test as generally performed is of limited usefulness and needs further refinement and standardization. Price made tests on 545 patients with untreated gonorrhea: according to him a positive result may be expected during the first week of the disease in 27 per cent of cases, during the second week in 46 per cent, during the third week in 70 per cent, during the fourth week in 88 per cent and during the fifth and sixth weeks in 100 per cent of cases. Location and anatomic spread of the disease notably influence the positivity of the test. After injections of gonococcal vaccines have been given to rabbits or nongonorrheal persons for four days results of the tests will be positive, will become very positive after 10 days of injections and negative six weeks after the injections are stopped. Price obtained positive tests in 80 to 90 per cent of cases of gonococcal arthritis, rheumatism or tenosynovitis.

Using this test as an index to the relative value of sulfonamide compounds Price concluded that protosil album (sulfanilamide) prevented the appearance of a positive test more effectively than uleron. Weiss and Arnold advised use of larger quantities of patient's serum than are generally used: thereby the sensitivity and stability of the test were notably enhanced without increasing the number of nonspecific and anti-complementary reactions.

[More data on incidence of false positive tests in persons without gonorrhea are needed. —Ed.]

*Comparative Value of Smears, Cultures and Complement Fixation Tests.* From a study of 100 women with chronic gonorrhea Jacobsen, Mason and Arnold concluded that in such cases cultures are superior to direct smears, and fixation tests are superior to either cultures or smears. Urethral smears were "positive" in only 3 per cent, "doubtful" in 16 per cent, "negative" in 81 per cent. Cervical smears were positive in 4 per cent, doubtful in 16 per cent, negative in 80 per cent. Cultures from urethra were positive in 13 per cent, from cervix in 17 per cent. Gonococcal complement fixation tests were positive in 32 per cent. Of the 100 cases "10 were positive by bacteriology and serology, 12 positive only by bacteriological methods, and 21 positive only by the complement fixation test."

The comparative value of cultures (modified McLeod method) and smears on 245 adult female patients was studied by Carpenter, Leahy and Wilson. The cultural method was found to be 191 per cent superior to the smear method. However, in 8 per cent of cases cultures were negative but smears were positive. Therefore, both tests should be used whenever possible. The combination of both tests was 208 per cent superior to the smear method alone. Stout and Todd also noted the superiority of cultures over smears.

These laboratory tests are therefore of considerable value in confirming the clinical diagnosis of gonorrhea and gonorrheal arthritis. But when laboratory tests are negative in the presence of clinical data highly suggestive of gonorrhea full significance should be given the latter, and therapeutic tests should be promptly instituted regardless of negative laboratory tests.<sup>535</sup>

4. *Tests of Bactericidal Power of Blood and Synovial Fluid.* Spink and Keefer<sup>518, 897</sup> continued their studies<sup>5</sup> on the bactericidal power of blood and synovial fluid for gonococci. In some cases of gonorrheal arthritis no gonococci can be recovered from synovial fluid; in these the prognosis for articular recovery is better than in cases in which gonococci are present in synovial fluid. Several factors operate to allow or prevent infection of the synovial cavity. One of them is the degree of

inflammation present: if the inflammation in subsynovial and synovial tissues is severe enough to destroy parts of the membrane, bacteria gain access to synovial fluid. Other factors are the number of infecting organisms and the antibody response. During gonorrhea specific antigonococcal antibodies develop, become present in blood, and diffuse into synovial fluid. Sometimes the concentration of antibodies in synovial fluid is equal to that in blood; at other times it is less. According to Spink and Keefer gonococci are first "sensitized" by antibody and then their destruction is completed by complement. When the antibody titer of both blood and synovial fluid is high, gonococci that reach the articular cavity are killed, and synovial fluid is kept sterile. When the antibody titer of blood, and consequently of synovial fluid, is low, gonococci will survive in synovial fluid. In some cases the antibody titer of synovial fluid is low and the fluid is therefore not bactericidal, even though the blood possesses a high antibody titer and is actively bactericidal. Since gonococci seem to thrive in regions supplied by large amounts of mucus (urethra, vagina, conjunctivae, joints, tendon sheaths) Keefer and Spink suggested that mucin either favors the growth of gonococci or somehow prevents their destruction by tissue antibodies. They studied the effect of adding mucin to whole blood of patients with gonorrheal arthritis, normal persons and rabbits. The addition of mucin to defibrinated blood depressed the bacteriolytic titer of the blood for gonococci. These results suggest that synovial mucin does not lower the amount of complement in synovial fluid or interfere with the action of complement. But apparently in some way as yet not clearly understood, mucin protects gonococci from the action of antibody unless a large amount of antibody is present.

[One of us, W. B., has observed that the blood from nongonorrheal patients may show the same variations in bacterial killing power to various gonococcal strains as do patients with acute or chronic gonorrhea, with or without complications. Repeated examinations at regular intervals for as long as six months failed to reveal any increase in the bacterial killing power.—Ed.]

5. *Concentration of Vitamin C in Blood.* While comparing the concentration of vitamin C in the blood of patients with atrophic arthritis to that of normal persons and other controls Rinehart and his colleagues obtained low values for vitamin C in plasma in 13 cases of gonorrheal arthritis. Normal values ranged from 0.22 to 1.45 mg. per 100 c.c. of plasma and averaged 0.7 mg. The plasma values for vitamin C among gonorrheal patients ranged from 0.09 to 0.64 mg. (average 0.22 mg.), indicating a definite vitamin C deficiency. Perhaps this deficiency was the result of the infection, for infection depletes the organic reserve of vitamin C. Another suggestion was offered: perhaps the vitamin deficiency was primary, and lowered the resistance of joints to subsequent bacterial invasion.

[Concentrations of vitamin C in blood are low in most patients with any debilitating disease.—Ed.]

## TREATMENT OF GONORRHEAL ARTHRITIS

The two most effective methods of treating gonorrheal arthritis continue to be fever therapy and sulfanilamide, either used alone or in combination. Although use of sulfanilamide or related compounds has largely supplanted use of fever therapy, certain cases of gonorrhea and gonorrheal arthritis are resistant to sulfanilamide, and hence are still suitable for fever therapy. Therefore it seems important to review current papers on fever therapy reporting work chiefly done before the use of sulfanilamide became general.

## FEVER THERAPY FOR GONORRHEAL ARTHRITIS

Eleven papers reported the results of fever therapy in about 560 cases of gonorrheal arthritis. Bauer and Cecil treated 71 cases: (24 acute, 39 subacute, 8 chronic). Complete symptomatic relief was noted in 12 acute, 18 subacute and 2 chronic cases; 10 acute, 12 subacute and 4 chronic cases were greatly improved. The rest were not benefited significantly. Results in Bierman and Levenson's 40 cases were "satisfactory and frequently dramatic"; in 32 "cure" was effected but in 9 physical therapy was needed to restore normal articular motion; in 8 improvement occurred but these were classed as failures because genital cultures remained positive. Among 40 cases of pelvic gonorrhea treated by Darling, Berris and Newman were 5 cases of gonorrheal arthritis. Results of fever therapy in the arthritic cases were not given separately, but of the 40 patients a total of 82 per cent were cured; 3 with one fever session, 25 with 2 sessions, 5 with 3 to 8 sessions. Seven patients (18 per cent) were unable or unwilling to continue treatment until cured.

Egan and Piaskoski treated 29 acute and 6 chronic cases of gonorrheal arthritis. Of the patients with acute gonorrheal arthritis 25 (86 per cent) were "completely relieved" by one to three fever sessions of 4 to 5 hours each at 106 to 107° F. Of the 4 patients not cured, 3 were "improved," one was slightly improved. In the 6 chronic cases duration of the disease was "from two months to many years"; none of the patients was cured; only 3 were improved. Sixteen patients with gonorrheal arthritis (stage unstated) were given hyperpyrexia by Gurnee: all were "uniformly benefited, being listed on discharge as 90 to 95 per cent improved." Only one fever session was required in 8 cases, two sessions in the rest. Combined general and pelvic heating was used. Of Owens' 30 patients 70 per cent were "cured," the rest "improved."

Purcell treated 2 acute cases: after one treatment relief was complete in one case, marked in the other. Of Schmidt's 7 patients, 6 were "promptly improved." Solomon and Stecher reviewed their results in 103 cases (84 acute cases, i.e., less than 8 weeks in duration and 19 chronic cases in which articular symptoms had lasted for months to seven years). [We do not believe that provable cases of gonorrheal arthritis remain active for more than a few weeks, certainly not for years, although residual deformity and stiffness may remain for years.—Ed.] Relief was complete in 52 per cent, partial in 30 per cent, insignificant in 18 per cent. Failures were often due to the patient's unwillingness to continue treatments. The average duration of the arthritis of patients completely relieved was 7.2 weeks, of those partially relieved, 11.7 weeks, of the rest 9.6 weeks.

Excellent results were also noted by Trautman, Stroupe and Devlin who treated 61 cases (37 acute, 24 chronic). Complete recovery or marked improvement was noted in 84 per cent of the acute and in 54 per cent of the chronic cases. Associated genital infections were cured thereby in 86 per cent of the acute and in 75 per cent of the chronic cases. In the acute cases

all of the patients who were not cured were moderately improved. Of the other 11 chronic cases 6 patients were moderately improved, 5 were slightly improved or not benefited. For all these cases an average of 7 to 8 fever sessions (each 5 hours at 106 to 107° F.) was required, a greater number than prescribed by many workers.

The true value of fever therapy in gonorrheal arthritis has been difficult to assess because some patients tend to recover spontaneously and rather rapidly, and because most workers have not compared their results from fever with those from less strenuous methods. Hence the second report of Schnabel and Fetter<sup>5, 839</sup> with controls is of special interest. Cures were obtained in 68 per cent of 70 acute cases treated with fever therapy but in only 6 per cent of 70 acute cases treated otherwise (old methods: local chemotherapy and physical therapy). The average period of hospitalization for treatment was 21 days in the first group, 39 days in the second. Cures were also obtained in 26 per cent of 23 chronic cases treated by fever but in only 4 per cent of 23 chronic cases treated otherwise. The average period of hospitalization for treatment was 33 days for patients given fever, 143 days in those treated otherwise. These statistics certainly indicate the superiority of fever therapy over older methods.

*Summary.* These reports present further evidence that complete cures are obtained in 70 to 90 per cent of acute cases and in about 60 to 80 per cent of chronic cases of gonorrheal arthritis in which from two to four (occasionally six or eight) fever sessions are used. The fever sessions almost uniformly consisted of five or six, occasionally seven, hours at 106 to 107° F. (rectal) given every two to four days.

[Fever therapy can only arrest the active disease; it cannot restore tissues already damaged, therefore it should be used early if at all.—Ed.]

### FEVER THERAPY FOR NONARTICULAR GONORRHEA

In the arthritic cases mentioned fever therapy generally controlled the genitourinary infection also. In some cases genital cultures or smears remained positive after articular symptoms disappeared, and two or more extra fever sessions were required. Occasionally fever therapy failed to cure the genital infection even though it cured the arthritis. In addition to the reports noted several other papers summarized the results of fever therapy for nonarticular gonorrhea.

Bierman and Levenson and Bierman and Horowitz treated 165 cases of gonorrhea. Of 125 women 93 per cent became free of gonococci after an average of 1.9 fever sessions (each 10 to 12 hours; combined general and pelvic heating). Of 40 males 70 per cent became free of gonococci after an average of 2.8 treatments. Failures were due to inadequate heating, or occasionally to the heat resistance of certain strains. As a result of their experiences with 95 cases of acute and chronic gonorrhea Egan and Piaskoski stated that "fever therapy will quickly and permanently cure gonorrhea and its complications in over 90 per cent of patients who are willing and able to undergo adequate treatment." [However, about 10 to 20 per cent of patients will not accept a full series of fever sessions.—Ed.] Of Gurnee's 79 cases of acute genital gonorrhea treated by a combination of hot box and Elliott treatments 84 per cent were cured by one or two fever sessions. Of 150 women with pelvic gonorrhea to whom Horowitz gave combined pelvic diathermy and systemic fever therapy, 92



per cent were freed of gonococci. When Horowitz had perfected the technic by which his last 73 cases were treated, over 60 per cent required only one treatment.

Krusen and his colleagues<sup>554, 556, 789</sup> favored the use of one 10 hour session of fever combined with pelvic diathermy instead of the usual successive short fever sessions. At times more than one session was required. Of patients with positive cultures, 95 per cent were cured after one or more sessions of fever. In 76 per cent of 95 cases treated by a single 10 hour session cultures became negative.<sup>554</sup> Of 266 patients studied by Krusen, Randall and Stuhler and given one to 13 sessions of fever (each 5 to 12 hours at 106.7° F.) 246 (93 per cent) obtained negative cultures and all were clinically improved. In another series of 31 cases given a single 10 hour session of general fever combined with additional pelvic heating (vaginal diathermy or Elliott method) 94 per cent gave consistently negative genital cultures after a single 10 hour fever session.<sup>789</sup> Excellent results from fever therapy in various types of genital and pelvic gonorrhea were also reported by Davis, R. Kovacs, Owens, Paul, Purcell, Schnabel and Fetter and by Trautman, Stroupe and Devlin.

### FEVER THERAPY FOR SPECIAL COMPLICATIONS OF GONORRHEA

1. *Gonococcal Endocarditis.* This is generally fatal. There are 139 cases reported in the literature; in the 108 "proved cases" collected by Freund, Anderson and Lilly the mortality was 94 per cent. The clinical and diagnostic features of the 7 recovered cases of gonococcal endocarditis were summarized. Freund, Anderson and Lilly reported an additional case in which fever therapy resulted in cure. A negress, aged 20 years, had gonococcemia and cardiac findings consistent with a diagnosis of acute endocarditis. The patient was given six fever sessions totalling 30 hours at 106 to 107.4° F. Fever, acute arthritis and cardiac abnormalities disappeared; cervical smears became negative and remained so four months thereafter.

[There is no certain method of diagnosing gonococcal endocarditis during life. Some "cured cases" may have been cases of gonococcal bacteremia without true gonococcal endocarditis.—Ed.]

2. *Gonorrheal Arthritis Complicating Pregnancy.* Acute gonorrheal arthritis occasionally complicates pregnancy. Upton, who reviewed the subject, considered fever therapy dangerous in such cases "since the products of conception always suffer, and death of the fetus may occur." However, Gurnee treated two cases of gonorrhea complicated by early pregnancy by combined pelvic and general hyperthermia. Each patient required three treatments. Neither patient aborted. One was cured, the other was not.

[How were the babies?—Ed.]

### GENERAL REMARKS ON FEVER THERAPY

*Preferred Methods.* Several workers<sup>336, 839, 889, 962</sup> preferred to give several short (5 to 7 hour) sessions with a Kettering Hypertherm. Zeiter used an unnamed heated humidified cabinet. Inductothermy seemed preferable to Castleden, and Heald. According to Phillips forms of penetrating heat (e.g., short wave electromagnetic induction) are physiologically superior to radiant heat. Osborne and Markson preferred the use of high frequency currents as safer and more comfortable than external heat; the former produces less alkalosis, a slower pulse, and preserves the natural heat gradient of the body which external heat does not. Schmidt preferred a cabinet equipped with vaporized hot water at a temperature of 130° F. arranged so that a cold spray could be applied at any time to cool the skin. The superiority of the combined technic (general fever plus additional pelvic heating) was upheld by several. For pelvic heating Gurnee favored the Elliott method; Bierman and Levenson, Horowitz, and Krusen and his colleagues preferred vaginal diathermy as being easier to

give and more comfortable for patients. Horowitz, and Krusen and his colleagues favored the use of one or two fairly long (10 to 12 hour) sessions of general fever, with pelvic heating to 109 to 112° F. (rectal). Krusen and his colleagues produced general fevers to 106.7° F. but Horowitz considered that a temperature of 105.5 to 106° was sufficient in view of the added local heat, and considerably easier and safer for the patient. The use of "low fever" (1° F. less than usual) supplemented by the inhalation of 50 to 80 per cent oxygen was found to be less effective than the usual amounts of fever (Krusen, Randall and Stuhler). The latter seemed to be slightly more effective when combined with oxygen therapy but results were not sufficiently better to continue the additional procedure. Darling, Berris and Newman found it inadvisable to combine local pelvic heating and systemic hyperpyrexia, because of their inability to gauge patients' temperatures accurately. Mouth temperatures were inaccurate because iced saline solution was constantly given; rectal temperatures do not indicate the amount of general fever. Randall, Krusen and Bannick recommended the following special preliminary preparation: the patient's skin is exposed to an ultraviolet lamp until a mild erythema is produced, then he is immersed in the Hubbard tank for 30 minutes, then wrapped in blankets for 1½ hours prior to the fever session. "The vasodilation thus secured aids the patient in tolerating the prolonged fever treatment." The intravenous injection of 5 per cent solution of dextrose in physiologic saline solution just after treatment was also considered desirable. Elkins described the arrangements and equipment required for a good fever therapy department.

Carpenter, Boak and Warren again stated their belief that the most rational method was to determine the thermal death time of each patient's gonococci and give one long (8 to 24 hour) fever session at 41.5° C. The thermal death time of 250 strains of gonococci recovered from various tissues varied from 6 to 34 hours at 41.5° C., but was between 11 and 21 hours for 75 per cent of the strains. No correlation was found between the thermal death time of the gonococcus and either the site of infection or severity of symptoms (virulence of invading strain).

[Few physicians have the facilities for rapidly determining the thermal death time of individual strains, and few patients are willing to endure such long sessions. The use of one or two 10 hour sessions seems to be a successful compromise.—Ed.]

*Physiologic Effects.* These effects were similar to those given in previous Reviews.<sup>406, 540, 790, 837, 885, 886</sup> Reactions indicating impending vascular collapse and shock were described.<sup>888</sup> Also reported were studies on the acid base balance,<sup>237</sup> and on the changes in blood volume and water balance which indicated the need of giving plenty of fluid during fever therapy to avoid shock.<sup>361</sup> Additional studies reported at the First International Conference on Fever Therapy (1937) were reviewed.<sup>552</sup> Studying psychologic and psychiatric reactions to fever therapy Ebaugh, Barnacle and Ewalt noted an exaggeration of patients' outstanding personality patterns. Phlegmatic patients were unperturbed and coöperative; aggressive persons became more aggressive and restless; contented sociable persons became elated and even euphoric during hyperpyrexia; pessimists exhibited deepened dissatisfaction with everything in general, and hypochondriacs were greatly concerned with their physical state. Emotional conflicts associated with certain diseases played a rôle in the patients' reactions to the treatments. Patients with gonorrhea commonly exhibited anxiety, fear and depression. Some patients with chronic arthritis, long sufferers with pain and invalidism, exhibited depression and hypochondriasis; others, however, appeared composed, congenial and even elated. Choreic children were emotionally unstable but were not anxious or apprehensive. Delirium was studied as it appeared in 350 patients during fever therapy: 390 episodes of delirium occurred; 104 gonorrheal patients had 170 such episodes, 35 patients with atrophic arthritis had 17, and 45 choreic patients had 12; the rest occurred in other cases. Episodes of delirium were materially reduced by psychotherapy, by increased experience with hyperpyrexia, and particularly by limitation of sedatives.

*Complications and Untoward Results.* Current statistics indicate again that when fever therapy is given in a hospital by a trained personnel it is essentially safe. Among 620 patients given over 2600 fever sessions at The Mayo Clinic there has been only one fatality.<sup>556</sup> Trautman, Stroupe and Devlin noted only one death (no details given) among 430 patients given 2597 treatments, but reported a few other untoward reactions: cardiovascular collapse in three cases, burns in one case, severe abdominal pain after treatment in one case, and an attack of grand mal after treatment of an epileptic. Kovacs reported no fatalities during 500 treatments given to an unstated number of patients. Friedman and Stettheimer reported the case of a child aged 2½ years with resistant acute gonorrheal vaginitis who died nine hours after the first and apparently well tolerated treatment (inductothermy; 8 hours at 106.6° F.). This death, the only one so far reported among children, resulted from circulatory failure and exhaustion of the heat regulating mechanism. They also noted (no details) the death of an elderly man with gonorrheal urethritis after hyperpyrexia. A choreic child given hyperpyrexia in a hot bath (2 to 3 hours in water at 120° F.) became unconscious and had convulsions; thereafter Lowenburg advised hot water temperatures at 105°, certainly not over 110° F. Gurnee disapproved of raising rectal temperatures to 106.7° F.: as a result of such treatments one patient died of heat stroke and two others had severe heat strokes with burns necessitating skin grafting. Since he adopted the combined heating method with mouth temperatures at 105° F. and vaginal temperatures at 115° (Elliott method) he noted no significant reactions except occasional mild vaginal bleeding. Gurnee abandoned the use of short-wave therapy to induce local pelvic heating because it produced some deep vaginal burns and vesicovaginal fistulas necessitating surgical repair; these did not occur with the Elliott method.

To prevent untoward reactions one must recognize signs of impending collapse (sudden increase in pulse rate; a rate about 160 or more; a sudden decrease of systolic blood pressure to 60 or 70 with an increase in diastolic pressure). To treat shock from fever therapy Solomon and Kopp removed patients from the fever cabinet, gave intravenous infusions of glucose 5 per cent and normal saline solutions, and gave inhalations of 5 to 7 per cent carbon dioxide in oxygen if respiratory embarrassment or tetany occurred.

#### CONCLUSIONS ON THE MERITS OF FEVER THERAPY FOR GONORRHEA AND GONORRHEAL ARTHRITIS

Because of the excellent results obtained, fever therapy was considered "virtually a specific for gonorrheal arthritis,"<sup>270</sup> and, "the quickest and most dependable method of curing gonorrhea."<sup>743</sup> At a round-table conference<sup>535</sup> of 23 genito-urinary specialists the consensus was that "properly used, fever therapy is probably the most effective form of therapy for gonococcal infections, but the cost of treatment and the limited number of hos-

pitals where the technic is safely and effectively used constitute its greatest limitation." One critic queried: "Is it logical to submit an average case to this severe treatment? Must we use a cannon to bring down a duck? The punishment of fever therapy in the male does not seem to fit the crime" (Strachstein). Others, however, regarded the misery which gonorrhea produces as "no small game" and considered fever therapy justified for patients who do not respond to the newer forms of chemotherapy. Nevertheless, although conceding the effectiveness of fever therapy, they criticized it as a time consuming, uncomfortable, generally strenuous and occasionally serious ordeal which, being a hospital procedure necessitating special attendants and the use of costly apparatus, is available only to a small percentage of patients. And of those who accept it from 8 to 30 per cent are unable,<sup>743</sup> unwilling or "too frightened" <sup>962</sup> to accept adequate amounts.

### SULFANILAMIDE: GENERAL CONSIDERATIONS

*Introduction.* Before discussing the use of sulfanilamide for gonorrhea and gonorrheal arthritis we will discuss the general topic of sulfanilamide and the newer concepts regarding it. The literature on sulfanilamide and related compounds has become voluminous indeed. From the publication of the first clinical report on the use of prontosil (Domagk, Feb. 15, 1935) until Nov. 1, 1937, 215 articles on sulfonamide compounds appeared.<sup>840</sup> The most significant of these were reported in our last Review.<sup>5</sup>

In addition to our synopsis which stressed clinical features, a number of short general reviews on sulfanilamide appeared during 1938.<sup>27, 68, 121, 128, 319, 390, 408, 515, 573, 688, 817, 852, 902, 1000</sup> Six reviews deserve special mention. Schulte reviewed concisely the early chemical and experimental work on the sulfonamide compounds. In five other reviews also ideas on the mode of action of these drugs, their toxicity, optimal dosage, clinical results, etc. were considered. That of Holman and Duff was the most comprehensive and contained 162 references to the literature of 1934 to 1937. McGinty considered all phases of sulfanilamide toxicity, and noted 164 references, mostly of 1937. Schnitker's review concerned 69 references to the literature of 1935 to 1937. Two excellent synopses included considerable material published in 1938; Garrod reviewed 166 reports (1934 et seq.) of which about 75 appeared in 1938, and Whitby reviewed 182 articles (1935 et seq.) about 100 of which appeared in 1938. Students of the subject can find the references to practically every significant report on the entire subject in these six useful reviews.

[Two recent books also review the entire subject: one by Long and Bliss, 1939, and one by Mellon, Gross and Cooper, 1938.—Ed.]

During 1938 several hundred papers on sulfonamide compounds appeared; we have reviewed herein only about 200 which seemed of special interest to physicians concerned with the use of these drugs to combat or prevent diseases of joints.

*Terminology.* Fortunately the approved terminology for these various drugs has been widely accepted, and the literature of 1938 spoke almost exclusively of sulfanilamide and not of its various synonyms (prontosil album, prontylin, etc.).<sup>5</sup>

*Mode of Action.* It is not yet known exactly how sulfanilamide acts against infection; hence its use is still largely empiric. The following modes of action have been suggested:

1. Sulfanilamide has a direct bactericidal effect on certain bacteria in vivo even though not in vitro. This idea suggested by certain earlier workers is still upheld by some current writers. When enough sulfanilamide was given, Farrell, Lyman and Youman found urine and prostatic secretions to be bactericidal to certain organisms (colon bacilli, *Staphylococcus aureus*); against these infections at least the drug acts directly in the urinary tract. A different view was held by Vest, Hill, Harrill and Pitts who frequently noted failures and successes in patients with equally high concentrations of sulfanilamide in blood and urine. They also noted marked reduction of urethral gonococci before there was much, sometimes even before there was any, sulfanilamide in urine. Hence they concluded that the drug acts on infections of the urinary tract through the blood stream and not solely in urine. Long (1937) did not believe the effect of the drug was primarily bactericidal. He and more recently others<sup>199, 350</sup> have noted no strong bactericidal effect of sulfanilamide in vitro or in vivo except perhaps in urines possessing high concentrations of the drug. However, Keefer and Rantz noted that the blood of gonorrheal patients receiving sulfanilamide, or normal blood to which the drug was added possessed bactericidal properties against gonococci. Studying the effect of the drug on various strains of gonococci, Cohn and Cohn and Peizer noted no bactericidal effect of sulfanilamide when gonococci were suspended in physiologic saline solution and injected intraperitoneally into mice, but they noted definite protection for mice infected with a gonococcus-mucin suspension.

2. Sulfanilamide possesses a bacteriostatic action on certain bacteria in vivo and in vitro. Most investigators agree that the drug somehow arrests bacterial growth, but are not agreed as to whether the action on bacteria is direct or indirect. Some workers believe that as a result of the bacteriostatic action of the drug, the rate of multiplication of bacteria is reduced; the bacteria cannot produce enough leukocidin and other bacterial toxins to inhibit phagocytosis by the leukocytes (Cokkinis and McElligott, Gay). But Britton was unable to demonstrate either bacteriolysis or bacteriostasis in vitro with sulfanilamide, proseptasine, soluseptasine, T 607 and T 626.

3. Sulfanilamide hinders capsule formation of bacteria. This idea is disputed.

4. Sulfanilamide activates the reticulo-endothelial system. This idea is also disputed.<sup>350</sup>

5. Sulfanilamide stimulates phagocytosis. A number of current investigators found no evidence to support this idea.<sup>205, 736, 737, 887, 989</sup>

6. Sulfanilamide aids phagocytosis indirectly; bacteria are "sickened" by the drug and rendered more susceptible to normal phagocytosis. Kolmer and his associates gave the drug to rabbits experimentally infected with beta hemolytic streptococci so that skin, blood and joints were infected. The drug usually increased phagocytosis of streptococci in local cutaneous lesions; hence it was concluded that its effectiveness depends in part on its ability to promote phagocytosis by inhibiting the growth and toxin-production of bacteria. Phagocytosis is a helpful but not essential factor (Lockwood).

7. Sulfanilamide activates opsonins. Finkelstein and Birkeland regarded the presence of serum essential for the drug to be effective in causing phagocytosis in vitro; "the serum-sulfanilamide complex acts as an opsonin to enhance phagocytosis." But Reimann saw no reason to confuse matters by introducing the word opsonin. Obviously when any drug inhibits bacterial growth, some of the bacteria will die and be taken in by phagocytes.

8. Sulfanilamide has a certain immunizing or detoxifying effect; it may neutralize such toxins as hemolysins and leukocidins. From their experimental work on

mice Carpenter, Hawley and Barbour concluded that sulfanilamide inactivates "gonococcal toxin." They noted that certain gonorrheal patients recovered with minimal concentrations of sulfanilamide in blood; others failed to respond to maximal concentrations; still others lost their symptoms but still retained viable gonococci. These facts suggested that the drug acts on bacterial toxins, not on bacteria themselves. Others noted no antitoxic effect from sulfanilamide.<sup>199, 479, 517, 527, 591</sup> It does not stimulate antibacterial immunity, does not neutralize streptococcal toxins (hemolysin, fibrinolysin, dermatoxin), does not affect the formation of antifibrinolysins, and does not prevent or delay the production of gonococcal complement-fixing antibodies.

9. Sulfanilamide inhibits the production of bacterial toxins. This view, held earlier by Long (1937), is supported by Cokkinis and McElligott and by Gay. According to Snowden and Ball the drug "controls gonotoxin." However, Gross, Cooper and Lewis, and Huntingdon reported that the drug does not significantly inhibit the formation of streptococcic hemolysin or fibrinolysin and does not affect the formation of toxins in vitro. If a drug inhibits bacterial multiplication it will naturally inhibit toxin production to a certain degree. Gay noted a decrease in the production, not of fibrinolysin or leukocidin, but apparently of hemotoxin. Hence to a limited extent sulfanilamide does inhibit the production of some bacterial toxins. According to Gay this inhibition permits certain defense cells, especially macrophages, to accumulate from the circulation and from local sources, and destroy the inhibited bacteria more readily.

10. Sulfanilamide operates by an electrophysical action: Green's hypothesis, unsupported by experimental data, is that sulfanilamide, like Congo red, may be effective because, carrying a negative electric charge, it neutralizes the bacteria carrying a positive charge.

11. That sulfanilamide causes bacterial "starvation" was advanced currently.<sup>346, 589-591</sup> The action of sulfanilamide is a delayed one, for a while after it is given bacteria actually multiply, according to Garrod; only later does bacteriostasis become evident. This suggested that the drug somehow interferes with assimilation of food by bacteria. Lockwood and his colleagues reported that when the drug was added to human serum, the serum became bacteriostatic for hemolytic streptococci. This bacteriostatic action could be prevented by adding small amounts of peptone. This suggested that the drug interferes with the ability of virulent hemolytic streptococci to use serum or tissue protein as food from which to obtain nitrogen. Without the latter the bacteria cannot multiply.

*Comment.* Arguments for and against these ideas were reviewed by several writers.<sup>27, 46, 319, 346, 461, 589, 798, 1027</sup> Obviously the mode of action of sulfanilamide is still uncertain. The controversy still revolves around the question whether under certain conditions sulfanilamide is bactericidal as well as bacteriostatic, whether phagocytosis is stimulated directly or merely indirectly assisted, and whether bacterial toxins are directly or indirectly inhibited or neutralized.<sup>643</sup> McGregor-Robertson studied the results of sulfanilamide therapy on gonorrheal partners: often one responded promptly, the other did not. It was assumed that the bacterial strains were identical. [Studies on the thermal death time of the strains were not made to certify that the partners' strains actually were identical. Sometimes they are not, as was shown by Boak, Carpenter and Warren.<sup>3</sup>—Ed.] If they had been identical these results would indicate that certain patients rather than certain gonococcal strains are resistant to sulfanilamide. Hence the drug acts, not directly on bacteria, but through the patients' defensive mechanism. But since the drug

does not augment the immunity mechanism specifically, Garrod advised, not the abandonment, but the supplemental use of the established methods of producing specific immunity (by serums, etc.).

*Absorption, Diffusion and Excretion of Sulfanilamide.* Marshall and his colleagues<sup>621, 623, 624</sup> reviewed previous, and reported new studies, on the absorption, diffusion and excretion of sulfanilamide and related compounds. Absorption is more rapid when sulfanilamide is given orally than when given subcutaneously. Diffusion is so readily accomplished that concentration of the drug in various body tissues and fluids is approximately equal. The relative amounts of sulfanilamide in blood, milk and cervical secretion were studied.<sup>10</sup> The drug appears in sweat; its concentration therein on hot days may be sufficient to reduce the urinary concentration significantly.<sup>442</sup> Several new and improved methods for determining concentrations of sulfanilamide in blood and other fluids were reported. Marshall and Litchfield, and Marshall and Cutting refined the original method of Marshall, Emerson and Cutting (1937) as did also Prom, Stevens and Hughes, and MacLachlan, Carey and Butler.

*Toxicity of Sulfanilamide: 1. Animal Experiments.* Studies on the relative toxicity of sulfanilamide in various animals were reported.<sup>621</sup> Free sulfanilamide is relatively nontoxic, its conjugated (acetylated) form is somewhat more toxic. Marshall, Emerson and Cutting provoked acidosis in dogs but noted no deleterious effect from sulfanilamide on the blood of dogs or rabbits, and no permanent renal damage although large doses produced transient renal insufficiency. Adair, Hesselstine and Hac noted the drug's harmful effect on the fetus of pregnant rabbits. A remarkably low toxicity of the drug for rabbits was noted by Kolmer and his colleagues: sulfanilamide provided to rabbits considerable, but not complete, protection against the development of experimental beta hemolytic streptococcic infections (including suppurative arthritis). Giving doses to rabbits comparable to those given to man, Kreutzman and Carr noted no significant effect on blood cells during treatment, but after treatment there was a 10 to 15 per cent increase in erythrocytes and in eosinophiles, moderate congestion of splenic pulp with erythrocytes, and an increase in the proportion of single-lobed eosinophiles in bone marrow: evidences of early depression of bone marrow.

*2. Toxic Effects of Sulfanilamide on Humans.* Another year's experience again indicates that sulfanilamide is relatively nontoxic to man. Serious reactions were rare but minor symptoms of toxicity were common. Most physicians reported that in a high percentage of their cases certain gastrointestinal and neurologic symptoms in variable amounts developed: cyanosis, lassitude, dizziness, faintness, grogginess, a "jittery feeling," tinnitus, headache, malaise, anorexia, nausea and sometimes vomiting. Often these symptoms lasted only two or three days and disappeared when the initial high doses of the drug were reduced.<sup>643, 683</sup> These symptoms were generally less notable among patients at rest in bed and rarely necessitated cessation of treatment but administration of the drug to ambulatory patients may have to be reduced or stopped. Because of the faintness, inability to concentrate, grogginess and disorientation developed by some ambulatory patients, such patients, particularly professional taxi or truck drivers and aviators, should be warned not to drive cars or fly.<sup>593, 643</sup> [Because of anoxemia sulfanilamide therapy lowers an aviator's "ceiling" by about 5000 feet. Hence passengers and air-craft employees are now prohibited from flying in England while under such therapy.<sup>325</sup>—Ed.] Such symptoms have already produced some automobile accidents.<sup>24, 841</sup> Young patients tolerate sulfanilamide better than the aged, males better than females. Children tolerate it very well.<sup>458</sup>

Toxic reactions have been classified<sup>1024</sup> as follows: (1) those which are due to a direct toxic effect of the drug and which generally vary with the dosage and the individual's tolerance (e.g., anorexia, nausea, etc.); (2)

those which are due apparently to individual idiosyncrasy (e.g., acute hemolytic anemia, agranulocytosis); these reactions bear little or no relationship to doses used; (3) those which result for unknown reasons and the significance of which is not clear: e.g., fever, skin rashes.

*Sulfanilamide Fever.* Of the more significant toxic reactions sulfanilamide fever was the commonest noted by Long and Bliss: it affected 6 per cent of 335 patients. Others noted it more often. Fever affected 50 per cent of the patients of Mahoney, Van Slyke and Thayer and in one rose to 105.8° F. within one hour of the (first?) dose of the drug but disappeared within 24 hours. A high fever affected 9 of Schoenrich's 60 patients, and 3 of the 115 patients of Vest, Hill, Harrill and Pitts. Fever was often accompanied by chills and rashes. Fever and chills affected 5 to 6 per cent of Ellison's patients. Generally fever of 102 to 103° F. was noted; occasionally it rose to 105 or even 106° F.<sup>46, 388, 591, 1024</sup> Fever was rare among children, frequent among adults.<sup>591</sup> Among Brown's<sup>128</sup> patients fever was noted, rarely before the third or fourth day, generally between the seventh and tenth days of treatment. Long noted its appearance anywhere between the first and fourteenth day of treatment. Some authors<sup>46</sup> recommended that when fever appears during sulfanilamide therapy administration of the drug should be stopped to see if the fever resulted therefrom; if so administration of the drug may be resumed cautiously if necessary. Others<sup>610</sup> stopped medication only if temperatures reached 101° F. Because early fever developed in cases in which dermatitis, acidosis, acute hemolytic anemia or agranulocytosis later developed, Long recommended that the development of even simple fever should be regarded as a warning, and administration of the drug stopped. When the fever has gone, one should give a test dose of 5 grains; if no reaction occurs within 12 hours, it is probably safe to resume treatment.

*Gastrointestinal Symptoms.* Mild symptoms were common and did not necessitate discontinuing doses of the drug. Occasionally vomiting, severe diarrhea, or abdominal pain, generally in upper quadrants, was noted.<sup>591, 644</sup> When vomiting or diarrhea affects infants, administration of the drug should be stopped.<sup>11</sup>

*Jaundice and Hepatitis.* Two types of jaundice may occur during sulfanilamide therapy: that from mild or severe hemolytic anemia, and that from toxic hepatitis. In either case use of the drug should be discontinued promptly. Two fatal cases of jaundice and hepatitis,<sup>49</sup> two nonfatal cases,<sup>644</sup> a fatal case of toxic hepatitis, jaundice and toxic erythema,<sup>828</sup> a fatal case of acute yellow atrophy in a patient who took more of the drug than prescribed,<sup>191</sup> a fatal case due either to the drug or to a coincidental biliary cirrhosis<sup>892</sup> were reported. Garvin noted five cases (two fatal) of toxic hepatitis reported in the literature and recorded five cases of his own (one fatal); in two of his cases and in one case previously reported exfoliative dermatitis was also a complication. Among 335 patients given sulfanilamide Long noted only one who had jaundice not arising from anemia. Rimington noted increased porphyrinuria in 8 of 12 patients on sulfanilamide. Rats so treated excreted 2 to 10 times the normal amounts of porphyrin in urine. Photosensitivity was also observed. The porphyrins isolated were coproporphyrins I and III. The latter was interpreted as indicating hepatic damage.

*Cardiac Symptoms.* Precordial pain was frequently noted and was generally relieved by rest in bed.<sup>960, 989</sup> A patient of Dozzi took 80 grains of sulfanilamide at one dose for a hemolytic streptococcal sore throat: joint pains developed the next day and four days later nodal rhythm which lasted four months.

[Were symptoms due to the drug or the infection?—Ed.]

*Renal Symptoms.* Long noted no renal disturbances, but others noted two cases of hemoglobinuria<sup>591</sup> and four cases of "chemical pyelitis."<sup>435</sup>

*Neurologic Reactions.* These included toxic psychosis, mild paranoia with audi-



tory and visual hallucinations,<sup>459</sup> disorientation and even mania in a few cases,<sup>591</sup> paresthesia,<sup>983</sup> dizziness and short loss of consciousness,<sup>351</sup> transient optic neuritis<sup>185</sup> hiccoughs with fever,<sup>1053</sup> peripheral neuritis with the clinical picture of progressive muscle dystrophy,<sup>730</sup> severe vertigo, dizziness, and ataxia with a positive Romberg sign in one case<sup>388</sup> and grogginess or disorientation of ambulatory patients sufficient to cause automobile accidents.<sup>24, 841</sup>

*Skin Rashes.* Morbilliform or maculopapular rashes frequently occurred, generally with fever.<sup>11, 35, 185, 611</sup> They occasionally affected infants after a single dose of the drug.<sup>11</sup> The incidence of such rashes among patients receiving the drug was reported variably to be 1,<sup>593</sup> 2,<sup>989</sup> 4,<sup>591</sup> 10,<sup>841</sup> 13,<sup>610</sup> 16,<sup>1024</sup> and 20<sup>435</sup> per cent. The rashes were often mild, occasionally severe and generally appeared between the eleventh and twenty-fourth day of treatment.<sup>1024</sup> In one case rash with edema of face and extremities, hemorrhagic spots and later desquamation developed.<sup>1024</sup> A case of "severe intractable ulcerative dermatitis" was encountered.<sup>410</sup> If the rashes are mild, treatment need not be stopped. If they are more marked use of the drug should be discontinued. Then the rashes usually will disappear promptly and may not reappear when the drug is given again.<sup>185</sup> One case deserves special mention. Rogers saw a woman who had had five minor operations performed under local anesthesia. The anesthetics were procaine hydrochloride, tutocain and butyn; all contain aminobenzene. After each of the last three operations allergic reactions appeared at the sites of injection of the anesthetic. Years later sulfanilamide (25 grains within 36 hours) was given orally for erysipelas. In the succeeding one to 10 days an acute reaction of bright red erythema, itching, swelling and tenderness appeared at the site (dermal and mucosal) of each previous injection of anesthetic. Sulfanilamide also contains aminobenzene to which the patient apparently had become sensitized. This form of allergy differed from food allergy in that the reaction occurred only in regions previously sensitized.

*Articular Reaction.* Nandi gave 10 grains of sulfanilamide t.i.d. to a young woman as a prophylactic measure after manual removal of placenta. Three days later her knees became painful; after three more days effusion developed, and ankles were painful. Fever and leukocytosis were present. A history of previous rheumatism was denied. Administration of the drug was stopped; the articular symptoms were reduced the next day and disappeared in three days.

[This was believed to represent a new and bona fide reaction to sulfanilamide. But is it not possible that mild articular infection occurred?—Ed.]

*Acidosis.* In 3 per cent of their cases, Long and Bliss noted "clinical acidosis" (hypernoia and lowered CO<sub>2</sub> combining power), associated with loss of sodium and potassium in urine. It could be prevented by the daily use of sodium bicarbonate in doses a third to a half that of the sulfanilamide. Strauss and Southworth noted a decrease in the CO<sub>2</sub> combining power of plasma, definite diuresis and an increased excretion of sodium and potassium among men given sulfanilamide. Even though large amounts of the drug were given to dogs loss of base through renal excretion was slight and always insufficient to alter the CO<sub>2</sub> combining power of plasma.

*Cyanosis.* This may result from (1) the presence of aniline black, a black oxidation product of sulfanilamide, (2) methemoglobinemia, (3) sulfhemoglobinemia. Cyanosis of variable degree affects most patients receiving the drug; its intensity usually varies with the doses used. It affects 20 per cent of children and from 50<sup>591</sup> to 75 per cent<sup>1024</sup> of adults under treatment. It is rarely due to methemoglobinemia or sulfhemoglobinemia, and cyanosis per se (without dyspnea) is not an indication to discontinue treatment.<sup>593, 621, 1024</sup> Fifteen cases of notable cyanosis without methemoglobinemia or sulfhemoglobinemia were reported.<sup>90, 180</sup> In eight such cases King and Leslie found the oxygen saturation of blood to be normal; hence oxygen therapy should not be expected to influence the cyanosis. Mull and Smith noted a case of marked cyanosis in which oxygen saturation of blood decreased from 88 to 39.8 per

cent; the oxygen capacity also dropped, but no sulfhemoglobinemia or methemoglobinemia was present. Ottenberg and Fox noted that irradiation of dilute solutions of sulfanilamide with ultraviolet light caused the development of a purple color which stained cells similarly to the hue of patients receiving the drug: perhaps a similar process causes the cyanosis in vivo.

*Methemoglobinemia.* This often occurs to some degree. It need not necessarily interfere with treatment. Even when marked, it disappears rapidly when administration of the drug is stopped. Oxygen therapy is helpful.<sup>1024</sup> Posner, Guthrie and Mattice noted four cases of cyanosis associated with an unstable methemoglobin in the blood which persisted during oxygen therapy but disappeared when sulfanilamide therapy was discontinued.

[Methylene blue given intravenously or orally will cause prompt disappearance of the methemoglobin (W. B.).—Ed.]

*Sulfhemoglobinemia.* This condition is more dangerous and persistent than methemoglobinemia. It may be evidenced by cyanosis and dyspnea. Administration of sulfanilamide must be discontinued. Oxygen therapy is useless. Transfusions and intravenous injections of saline and glucose solutions are indicated.<sup>1024</sup> [Some do not now agree with this view.—Ed.] No new cases were reported.

*Leukocytosis.* Kracke noted leukocytosis (25,000 to 74,000) in 6 cases. Alpert and Forbes reported a case in which leukocytes numbered 32,000 before and 39,000 after a period of granulocytopenia (leukocytes 1200) from sulfanilamide. Leukocytosis was not noted by others.<sup>89, 90</sup>

*Leukopenia.* A transient polymorphonuclear leukopenia affected 23 of 50 ambulatory patients receiving the drug.<sup>122</sup> In Johnston's case leukocytes in the blood decreased rapidly to 3500. Others noted no leukopenia.<sup>89, 90, 435</sup>

*Hemolytic Anemia.* A mild (10 to 20 per cent) reduction in hemoglobin, unassociated with bilirubinemia, was commonly noted.<sup>11, 593, 610, 960</sup> Such mild reductions do not necessitate cessation of treatment.<sup>46, 593</sup> Severe acute hemolytic anemia is one of the rare and serious toxic reactions. Vest, Harrill and Colston noted 18 nonfatal cases among 800 to 900 patients treated at Johns Hopkins Hospital, and 2 nonfatal cases among 300 patients at Brady Institute. Acute hemolytic anemia affected "a few" of the 250 patients of Lockwood, Coburn and Stokinger, 3 per cent of Long's 335 patients and 4 per cent of Wood's 522 patients. The condition appeared generally 24 to 72 hours after treatment was begun. Six nonfatal cases were reported.<sup>364, 515, 697, 815, 902, 960</sup> The lowest hemoglobin noted was "less than 25 per cent" <sup>364</sup>; in two cases the erythrocyte count fell to about 1,000,000 cells.<sup>364, 515</sup> In one case, only 30 grains of sulfanilamide had been taken.<sup>515</sup>

In such cases administration of the drug must be stopped at once, the intake of fluid should be large; transfusions are generally required. Bone marrow (oral), and liver extracts have been prescribed. Sometimes if patients are "alkalized" (no details) and "fluids are forced" transfusions may be unnecessary, according to Vest, Harrill and Colston.

Heretofore no fatality from acute hemolytic anemia caused by sulfanilamide has been noted. Wood reported the death of a negro from acute hemolytic anemia which developed during administration of the drug. The patient had hemolytic streptococcal infection which possibly may have been a factor in producing hemolysis, but the infection had subsided clinically during therapy. The pathologic findings were representative of any severe hemolytic anemia; no feature was considered a specific lesion from the drug.

*Agranulocytosis.* This represents an idiosyncrasy which has occurred generally on ordinary doses of the drug. It is often fatal: 7 of the 10 cases reported in 1937 were fatal. Fifteen new cases were reported: 10 of them were nonfatal, recovery occurring after the use of pentnucleotide, roentgen therapy over long bones, whole

blood given intramuscularly and concentrated yellow bone marrow.<sup>22, 23, 499, 502, 591, 593, 645, 987</sup>

Included in the 10 nonfatal cases were 2 occurring among 800 to 900 patients on sulfanilamide observed by Vest, Harrill and Colston, and one case among Long's 335 patients. Five fatal cases were reported.<sup>77, 126, 230, 719, 847</sup> Synopses of cases previously reported were made.<sup>22, 499, 548, 643</sup> In the nonfatal case of Allen and Short an absolute monocytosis began five days after circulating neutrophils began to diminish and continued through the period of neutropenia. This was regarded as a sign of favorable prognosis since Rosenthal and Abel (1936) noticed that fewer deaths occurred from neutropenia when it was associated with an absolute increase in monocytes.

*"Elixir sulfanilamide—Massengill."* Further comments on this disaster appeared.<sup>969</sup> Another fatality from the "elixir" was noted.<sup>629</sup> Necropsy findings in several cases were reported.<sup>605</sup> Studies on the toxicity of the elixir for animals were made.<sup>760</sup> Deaths were due, not to sulfanilamide, but to the solvent used (diethylene glycol).

*Summary.* Physicians must be familiar with the protean toxic reactions to the drug and their relative seriousness, but this summary must not lead one to believe that the more serious reactions are frequent. At the Johns Hopkins Hospital no mortality occurred among 900 patients given sulfanilamide, and only one of a group of 115 ambulatory patients given the drug had to be hospitalized because of toxicity (Vest, Harrill, Hill and Pitts). West gave as much as 198 grains in one day and as much as 5000 grains over a period of weeks without noting any serious reaction. Womack cited Colston to the effect that only one death (agranulocytosis) had occurred among about 5000 cases of various diseases in Baltimore treated with sulfanilamide. But despite its being relatively nontoxic the drug is not a panacea and must be used with caution. The percentage of patients who cannot take adequate amounts of the drug because of annoying (but not necessarily serious) toxic effect was variably reported as being 5 per cent,<sup>280</sup> 5 to 10 per cent,<sup>987</sup> 8 to 10 per cent,<sup>208</sup> 13 per cent,<sup>24</sup> and 10 to 20 per cent.<sup>46</sup> As previously stated toxicity is usually more notable and more frequent among ambulatory patients than among those bedded at home or in hospitals. There was no relationship between the appearance of toxicity and the therapeutic effectiveness of the drug.<sup>591</sup>

*Treatment of Toxicity.* In the presence of mild toxicity (malaise, headache, nausea) full medication should be continued until the desired concentration in the blood is reached; when the quantity is reduced to a maintenance dose, these milder reactions generally disappear or become insignificant. In the presence of moderately severe toxic effect (skin rashes, diarrhea, abdominal pain) the dose of the drug should be reduced or continued with caution.<sup>924</sup> Some advise discontinuance of the drug for a few days to avoid more serious reactions. If mild or moderate toxic reactions do not disappear promptly when the drug is stopped temporarily, or if they promptly recur when use of the drug is resumed, sulfanilamide therapy should be abandoned in favor of other measures.<sup>49</sup> In the presence of severe toxic reactions (fever with tachycardia, acute hemolytic anemia, acute

leukopenia, jaundice) administration of the drug should be stopped at once, and large amounts of fluid given. Sometimes this will suffice but in most cases the special measures mentioned in connection with the individual toxic reactions are urgently required.

*Prevention of Toxic Reactions.* The safest way to prevent serious toxic reactions is for physicians to hospitalize patients whenever possible at least for the first week or two of treatment. Dosage can be controlled more accurately by frequent estimations of sulfanilamide in the blood. Minor toxic reactions are endured more easily. Major reactions often can be prevented or their earliest appearance detected by frequent (daily) estimations of level of blood cells and hemoglobin and close clinical observations on fever, condition of skin, etc.<sup>11, 593</sup> Some physicians stated that to prevent sulfhemoglobinemia patients should avoid eggs, onions, sulfur compounds, the saline and anthracene groups of aperients and laxatives (e.g., magnesium sulfate), aniline derivatives (phenacetin and acetanilid), the phenylhydrazine derivatives (antipyrine and aminopyrine) and the sulfonemethane group of drugs. If cyanosis is notable or associated with dyspnea, a spectroscopic examination of blood for methemoglobin or sulfhemoglobin should be made. [Sulfhemoglobinemia is a very rare complication: indeed some investigators doubt if true sulfhemoglobinemia ever results from the use of sulfanilamide; others doubt that it can be prevented by the measures noted.—Ed.] To prevent acidosis enough sodium bicarbonate should be given to make urine neutral or alkaline. Various doses of the alkali were recommended. Long gave a third or a half as much sodium bicarbonate daily as sulfanilamide; others prescribed equal amounts of alkali and sulfanilamide; some gave 10 grains of sodium bicarbonate with each dose of sulfanilamide; others withheld alkali until signs of intolerance appeared.<sup>280</sup> [One of us (W. B.) has been unable to prevent acidosis by the use of alkali and considers its use unnecessary.—Ed.] Noting a marked increase in mortality among litters of pregnant rabbits given sulfanilamide Adair, Hesseltine and Hac recommended that until more is known of the tolerance of the human fetus and of the newborn for sulfanilamide, the drug should be given only with the utmost caution during pregnancy and lactation. Mothers receiving the drug should cease breast-feeding while the drug is being excreted in their milk.

*Contraindications to Sulfanilamide Therapy.* No new ones were reported. In cases of marked anemia, leukopenia, renal disease or hepatic disease the drug should not be used, or, if its use is necessary, it should be given with caution.<sup>49</sup> Its use was not advised in acute rheumatic fever.<sup>630, 936</sup> Long and Bliss did not consider previous hepatic disease or jaundice to be necessarily a contraindication.

*Sulfanilamide as a Prophylactic.* As yet few studies have appeared on the prophylactic value of sulfanilamide in human diseases. Whitby considered it of no prophylactic value in gonorrhea. Britton regarded its use as a prophylactic in general medicine as unjustified unless there is some

reason to anticipate sepsis in an individual case. But Jones<sup>500</sup> recommended the prophylactic use of small doses of the drug by persons exposed to epidemics of meningococcal or hemolytic streptococcal infections, and others are reporting on its value in preventing recurrent rheumatic fever.<sup>194, 949</sup>

#### TREATMENT OF GONORRHEAL ARTHRITIS WITH SULFANILAMIDE

Although the effects of sulfanilamide on gonorrhea in general were reported in scores of papers, only two papers specifically dealt with results in gonorrheal arthritis. Bauer and Coggeshall gave "large doses" of the drug [daily dose,  $\frac{3}{4}$  grain per pound of body weight, but not over 120 grains in one day.—Ed.] to 14 patients with proved and 4 with "probable" gonorrheal arthritis. Nine (64 per cent) of the former and 2 (50 per cent) of the latter [61 per cent of the total] were "strikingly improved" 48 to 72 hours after treatment was begun. Infected synovial fluids became sterile promptly. No gonococci could be isolated from genital foci after the third day of medication. No relapses occurred. Final results were more prompt and satisfactory with this treatment than with older methods. The drug appeared to be "a specific chemotherapeutic agent." But the effective dose varied greatly: some cures were effected with 5 mg. per cent of free sulfanilamide in the blood; in other cases 10 mg. per cent or more was required. It was recommended that if definite clinical improvement is not noted 72 hours after starting "large doses," the dose should be increased. To maintain a constant level of free sulfanilamide in the blood, one-sixth of the total large daily dose was given every four hours, day and night and the intake of fluid was kept constant.

Simmons and Dunn treated 5 cases of gonorrheal arthritis with rest in bed and sulfanilamide (80 grains daily for two days, 60 grains for two days, 40 grains for seven days). Three patients were free of pain in two days and returned to work within 12 days. One patient was relieved promptly of all symptoms within 72 hours, but he then fell and injured the affected knee. The resulting effusion was not affected by sulfanilamide, rest and heat. Prolonged treatment for one year was required for complete recovery. One patient noted prompt and complete relief of arthritis, but apparently the genital focus was not cured. A month later an articular and pelvic exacerbation occurred which failed to respond to rest, local treatment and sulfanilamide, doses of which had to be small because of poor tolerance. She then was given 40 grains of sulfanilamide daily for three days followed by fever treatment (10 hours at 106° F.). Genital and articular symptoms promptly disappeared.

To obtain a broader view of the situation than that presented by these two short reports we reviewed about 50 papers on sulfanilamide therapy of gonorrhea and found the following scattered remarks about results in gonorrheal arthritis. Among 633 cases of gonorrhea treated by Cokkinis and McElligott were nine of gonorrheal arthritis in all of which cure occurred

within three weeks, two cases of "gonorrheal synovitis" which "yielded rapidly" to the drug, and eight of fibrositis six of which were cured within four weeks. These workers developed a special plan of sulfanilamide therapy which will be discussed later. Among Sorenson's 25 cases of gonorrhea were four of gonorrheal arthritis. The patients were given sulfanilamide: 80 grains for one day, 60 grains for one day, 30 grains for 10 to 25 days; three of the four patients were cured within four weeks. [No details of these cases were given. Results were not obtained very promptly.—Ed.] Stevens gave the drug (dose unstated) to four patients with gonorrheal arthritis: its use was discontinued in one case because of a toxic reaction. "Two cases did very well and the fourth case was benefited but not as quickly." Cook and Buchtel treated "a few cases" of gonorrheal arthritis: results were "variable." Daily dosage of sulfanilamide was 75 grains for two to three days, 60 grains for two to three days, then 40 grains for the remainder of the 14 days' course.

Six of the 158 patients with gonorrhea seen by Alyea, Daniel and Harris had gonorrheal arthritis. Sulfanilamide was generally given thus: 90 grains for one day, 45 grains daily for the next 13 days. The joints became "well" in one case, "much improved" in four cases and were unimproved in one case. Genital foci were cured in only two of these six cases. Admittedly estimations of sulfanilamide in the blood had not been done satisfactorily, hence no final conclusions as to the value of the drug in arthritis could be made. "Striking results" in two cases of gonorrheal arthritis were noted by Brunet, Reinhardt and Shaw, although small doses (not over 40 grains daily) were given. Such doses proved unsatisfactory to these physicians in the management of nonarticular gonorrhea.

Satisfactory and generally prompt (within 5 to 10 days) cures in single cases of gonorrheal arthritis were reported without detail by Adler, McGregor-Robertson, Nair, and Townsend and Mulcahy. Moderately large doses were used. King mentioned an unstated number of patients with gonorrheal arthritis "miraculously cured"; dosage was 80 grains for one day, 60 grains for one day, 30 to 40 grains daily "thereafter." Results in an unstated number of cases of gonorrheal arthritis treated by Clark and Branham were "disappointing"; the daily dosage was 60 grains for two days, 40 grains for five days, 30 grains for seven days.

[Little or no details were given concerning these cases. It will be seen that, although the full doses originally recommended by Long (1937) and by Colston, Dees and Harrill (1937) were occasionally used, most cases were treated by smaller doses which we believe are likely to be inadequate at least in some cases. Nevertheless when results in all these cases are summarized (in so far as they can be) it appears that in 38 (70 per cent) of 54 stated cases the gonorrheal arthritis was rather promptly cured; in 16 cases (30 per cent) it was either unimproved or improved but not cured by sulfanilamide.—Ed.]

Gonorrheal rheumatism developed in two cases of genital gonorrhea during treatment with sulfanilamide: in one instance "tenosynovitis" occurred,

but the patient was receiving rather small doses (60 grains daily for two days, 50 grains for six days, 45 grains for six days).<sup>887</sup> Despite fair sized doses (80 grains daily for two days, 60 grains for two days, 40 grains daily for eight days more) another patient on the eighth day of treatment developed arthritis, conjunctivitis, iritis and herpes zoster, and did not recover for five or six months.

[The exact value of sulfanilamide in the control of gonorrheal arthritis will not be known until many more cases have been carefully studied as to the presence or absence of intra-articular gonococci, and then properly treated with full doses of the drug. It is our opinion that the highest percentage of cures is obtained with levels of 10 to 15 mg. free sulfanilamide in 100 c.c. of blood.—Ed.]

### SULFANILAMIDE FOR NONARTICULAR (UROGENITAL) GONORRHEA

The early reports (1937) on the effect of sulfanilamide on gonorrheal urethritis were almost unanimously enthusiastic. Eight of these early reports were tabulated by Vest, Harrill and Colston as follows:

Author (1937)	Acute Gonorrheal Urethritis, Cases Treated	Satisfactory Results Obtained	
		Cases	%
Reuter	100	92	92
Herrold	30	15	50
Buchtel and Cook	21	19	90
Orr	104	92	88
Crean	100	90	90
Cokkinis	250	200 (estimation)	"80+"
Erskine	29	21	73
Watts, Oden and Gordon	72	58	80
Total	706	587	83

In summary, "satisfactory results" were obtained in 83 per cent of 706 cases. In contrast to the good results noted by the majority were the poor results of Herrold (1937), which Vest, Harrill and Colston attributed to inadequate dosage of sulfanilamide, and the "unsatisfactory" results reported by Anwyl-Davies (1937).

To see whether these early optimistic opinions were supported by the experiences of another year we reviewed about 50 later reports (1938) on the effects of sulfanilamide on urogenital gonorrhea. We have attempted to make a statistical summary of 46 of these recent reports (table 1). It is difficult to know how accurate such a summary can be or how much significance can be attached to it. There were many variables. Among the cases treated were all types of acute and chronic urogenital gonorrhea with and without complications. There was great diversity in the method of dosage and management of the cases. Standards of "cure" varied considerably. In some cases a "cure" was apparently based mainly if not solely on disappearance of symptoms, in other cases on relief of symptoms plus the appearance of (a variable number of) "negative" smears (not cultures). Some authors observed more rigid standards of "cure" and maintained a more satisfactory and longer follow-up period of observation before reporting a cure. (If this is not done patients and physicians will learn to their sorrow that "the most sensitive media or test of cure are the urethra of the husband and the eye of the child" [Rorke]). Despite these variables table 1 is given for what it may be worth and will at least give some idea of the present status of this form of therapy.

TABLE I

Results from Sulfanilamide in Nonarticular Gonorrhea (1938)

Reporter	Cases Treated	Cures Reported		Dosages Used L = large M = moderate S = small
		Cases*	Per cent	
Adler	36	28	78	L
Ainsworth	250	193	77	L
Alyea, Daniel and Harris	158	—	{ 75 acute 50 chronic	M
Bauer and Coggeshall	18	17	94	L
Benson	22†	4	18	—
Berry	50	Results disappointing		S
Brunet, Reinhardt, and Shaw	—	Expect 10 % cures		S
Burns	—	Results not good		S
Butler, W. W. S.	124	—	"About 75"	M
Chisholm	187	75	40	L
Clark and Branham	—	—	85	M
Cokkinis and McElligott	633	—	80-90	M
Ellison	100	68	68	L
Evans, K. L.	214	146	68	M
Goodwin	25	19	76	S
Grodberg and Carey	32	27	84	S
Harris	—	—	33	S
Hering	46	34	74	M
Herrold	50	17	34	M
Hoberg and Reck	50	28	56	M
Hoffman, Schneider, Blatt, and Herrold	25†	11	44	M
Holmes, Jones, and Gildersleeve	42†	8	19	M
Horowitz	12	7	58	M
King	87	—	"Under 10"	M
Mahoney, Van Slyke, and Thayer	205	174	85	L
Manor	33	28	85	M and S
McCuskey and McCuskey	80	56	70	M
McGregor-Robertson	100	75	75	L
Mitchell, D. R.	137	42	31	L
Nair	27	25	93	M
O'Hanlon	101	82	81	M
Randall, Krusen, and Bannick	16	15	94	M
Rock	40	32	80	S
Schoenrich	60	—	"Striking"	L
Shih and Hsiung	41	4	10	S
Sichel	35	25	71	S
Sinkoe	85	72	85	M
Snowden and Bell	15	8	53	S
Sorenson	25	22	88	M
Spink and Gaston	21	18	86	M
Spooner	33	15	45	M
Townsend and Mulcahy	90	81	90	L
Van Slyke, Thayer, and Mahoney	100	84	84	L
Vest, Harrill, and Colston	125	—	80+	M
Vest, Harrill, Hill, and Pitts	115	Expect 60% cures		L
Womack	—	—	40-50	M
Total	(3645)			
Total in which results were enumerated	2293	1540	67	

\* Number stated or estimated from percentage stated.

† Juvenile vaginitis.



Results were quite variable, "cures" being obtained in from 10 to 94 per cent, which is, to say the least, quite a spread! Because of incomplete data the total results of all the reports in table 1 cannot be estimated, but, summarizing the addable figures, there were 2293 cases of gonorrhea in 1540 or 67 per cent of which the patients were presumably cured. This figure is definitely, although not strikingly lower than that obtained by analyzing the small group of 1937 reports (83 per cent of patients cured). In part it probably represents a more critical appraisal of results, a swing away from overenthusiasm. But the two groups were not entirely comparable. During the early work (1937) with sulfanilamide most patients were hospitalized for close supervision of therapy by research investigators able to gauge the necessary dosage by estimation of blood sulfanilamide. The more recent figures concern large numbers of ambulatory patients not subject to as careful supervision. Since ambulatory patients generally cannot tolerate (or were not given) as much sulfanilamide as hospitalized patients, a distinct difference in dosage was apparent. Indicated in table 1 is our estimate of the dosage given by the various workers. Because of the great differences in the dosage schemes used, classification was often difficult. In general "large dosage" indicates the approximate use of those fairly high doses originally advocated by Long and Bliss (1937) and by Colston, Dees and Harrill (1937): full initial doses (generally 80, rarely 120 grains, daily) for the first few days; then a gradual reduction. "Moderate dosage" indicates the use of initial doses generally around 60 grains for three or four days and then a reduction, but also some instances are included in which 80 grains were given for only one day and then the dose was rapidly reduced to 30 or 40 grains. "Small dosage" indicates the use generally of initial and subsequent doses not more than 40 or 50 grains, sometimes never more than 20 grains, daily.

A survey of the individual reports tended to strengthen impressions based on our own experiences that best results are undoubtedly obtained when full dosage is applied. However, an analysis of table 1, rearranged according to dosage, does not of itself lend much proof for this belief. Of a total of 1223 patients presumably treated by large doses 837 or 68.4 per cent were cured. Of a total of 860 patients given "moderate doses" 584 or 67.9 per cent were cured, suggesting that there is no special merit in the use of full doses as results with moderate doses were almost identical. [But in these cases of gonorrhea the difference between "large" and "moderate" doses was not great. The large doses used in these cases were *not* the high doses used in more serious diseases.—Ed.] Of 188 patients given small doses 115 or 61.1 per cent were cured, a difference which is definite but not as striking as one might expect. These figures merely confirm observations noted in the discussion on treatment, to the effect that although full doses are generally more effective than small doses, other factors than dosage influence the end results.

*Poor Results, Failures and Comments Thereon.* Poorest results were noted in cases of juvenile gonorrheal vaginitis: results in three series were satisfactory in only 18, 19 and 43 per cent of cases.<sup>76, 458, 465</sup> A number of writers were pessimistic about their results. Thus Brunet, Reinhardt and Shaw do not expect cures in more than 10 per cent of cases of anterior urethritis (small doses of the drug, not over 40 grains a day, were used). Some<sup>10</sup> called the routine use of sulfanilamide for gonorrhea "unwarranted." Delighted with his preliminary successes in obtaining rapid symptomatic cures in "almost 100 per cent of cases," King noted such a dis-

couraging frequency of bacteriologic remissions that he condemned the sole use of sulfanilamide for gonorrhea as "extremely hazardous," productive of real or bacteriologic cures in only about 10 per cent of his cases (doses used: 80 grains for one day, 60 grains for one day, 30 to 40 grains daily thereafter). Shih and Hsiung obtained symptomatic cures in 56 per cent but bacteriologic cures in only 10 per cent of their cases. Likewise, Mitchell noted satisfactory relief of symptoms in 75 per cent, but bacteriologic cures in only 31 per cent of his 137 cases. Other reports were also rather pessimistic.<sup>80, 143, 185, 419, 438, 899, 1043</sup> These and other writers stressed the great danger that sulfanilamide therapy will foster many "false cures," and raise a great crop of gonococcal carriers in persons whose symptoms cleared so satisfactorily and promptly that they or their physicians discontinued medication before a true bacteriologic cure resulted. To avoid this danger physicians again stressed the importance of continuing to give sulfanilamide for several (generally 7 to 16) days after all symptoms have disappeared, and thereafter rigidly and repeatedly examining the patients by cultures (rather than smears) for gonococci and by provocative tests, and so forth, to uncover any symptomless bacteriologic recurrence which, if present, should be promptly treated by another course of sulfanilamide or otherwise. Jones<sup>504</sup> stated that the use of sulfanilamide had not [yet.—Ed.] lowered the general incidence of gonorrhea in the state of Washington; he warned that, because the drug changes the characteristics of gonococci seen in stained smears, physicians must now exercise greater care in taking, staining, and studying smears than ever before.

Reasons for failure can be summarized as follows: 1. Inability of some patients (10 to 20 per cent) to take adequate amounts of the drug.<sup>46</sup> 2. Insufficient dosage given to patients who could take full doses. Ambulatory patients are often given too small doses; if their dosage is ineffective they should be hospitalized for seven to ten days of full medication.<sup>989</sup> 3. Premature cessation of treatment; medication stopped two to seven days after symptomatic cure and not continued until bacteriologic cure is obtained. 4. Inadequate follow-up examination to detect uncured symptomless infection. Recurrences are likely because sulfanilamide does not raise a patient's immunity to gonococci, and too many gonococci in deep seated foci, e.g., submucosal glands, do not come in contact with the drug.<sup>542</sup> 5. Resistance of certain patients (or strains of gonococci) to sulfanilamide; even adequate or full dosage does not result in cure. Smears and cultures occasionally remain positive even when the concentration of free sulfanilamide in blood is 9.6 to 25 mg. per cent (Adler). Concentrations in the blood were about the same in 16 failures as in 16 successes.<sup>988, 989</sup> 6. Excretion of two forms of the drug in urine in abnormal proportions. Usually 80 per cent of the drug is excreted as free sulfanilamide and about 20 per cent as the conjugated (or inactive) form. Occasionally equal amounts of both forms are present. Some physicians<sup>24, 438</sup> conjectured that perhaps there is present in the blood and tissues of patients unresponsive to sulfanilamide an abnormally

large percentage of the inactive (conjugated) form. However, in one group not benefited by the drug normal proportions of the two forms of the drug were found in the blood.<sup>24</sup>

Additional reasons for failure were suggested by Cokkinis and McElligott: 7. In a high proportion of their cases classed as failures the patients had enlarged prostates. 8. A small proportion of failures were due to other local complications (e.g., urethral stricture; calculous prostatitis, Tyson's adenitis). 9. The most important cause of failure was believed to be improper timing in the use of the drug. Cokkinis and McElligott insist that a degree of immunity is essential for optimal results with the drug. Of factors influencing their results, the duration of the disease preceding treatment proved to be "by far the most important." Whereas "good results" were obtained in from 72 to 78 per cent of cases in which treatment was begun during the first seven days of the disease, similar results were obtained in 92 to 98 per cent of those cases in which medication was not begun until from eight days to six months after their disease began. Furthermore the frequency of relapses and complications decreased with increasing chronicity of the disease when treatment was begun. The marked improvement in results noted in cases not treated until early in the second week of the disease "could have only one explanation—that it takes that much time for the body to acquire enough immunity to dispose of the organisms arrested by sulfanilamide." Hence according to these writers it is inadvisable to use sulfanilamide too early in the course of the disease. The correct time to start treatment with sulfanilamide is the eighth to tenth day of the disease. Treatment during the first week reduces the chance of success from a single full course by 50 per cent and the chance of ultimate success (after an additional course) by 25 per cent. A somewhat similar view was expressed by Harrison, and others<sup>24</sup> agreed that a week's delay in treatment was not disadvantageous.

[This is an interesting concept; other investigators should restudy their results in the light of this. The statistics of Cokkinis and McElligott seem to have been carefully analyzed and the data as given by them make a forceful argument. But the studies of one of us, W. B., have failed to support this concept. Until it is proved, delay in instituting treatment seems unfair to the patient and productive of a greater incidence of complications.—Ed.]

*Good Results: Summary and Comment.* In contrast to the rather disappointing results just reported were the very good results noted by the majority, "cures" being frequently obtained in 75 to 85, occasionally even in 90 per cent, of cases treated. Writers spoke of the drug as of "inestimable value"<sup>208</sup> and of its results as "very striking," "dramatic," "very prompt and satisfactory," "remarkable," "almost miraculous." Best results were generally noted in uncomplicated urethritis. Differences of opinion existed as to whether acute or chronic gonorrhea was more readily controlled by sulfanilamide. According to one report<sup>24</sup> acute prostatitis responded much more readily (75 per cent of patients cured) than chronic

prostatitis (50 per cent cured). Chisholm's results in acute and chronic urethritis were equally good. According to Hering chronic gonorrhea of males responded better (88 per cent cured) than acute gonorrhea (66 per cent cured). Mitchell noted more "symptomatic cures" but fewer real or "bacterial cures" in acute than in chronic cases.

Three control studies were of interest. Steele-Perkins stated that 50 patients treated by older methods required an average of 89 days, whereas 50 patients given sulfanilamide required an average of only 32 days to obtain satisfactory results, and there were fewer complications in the latter group. Scarcello's 105 patients were divided into three groups: those given "irrigation treatments" took about twice as long and those receiving Corbus-Ferry vaccine took almost three times as long to be cured as those given sulfanilamide. McGregor-Robertson treated 100 patients with acute uncomplicated gonorrheal urethritis with irrigations (65 per cent were cured) and 100 with sulfanilamide alone (60 per cent were promptly cured). Results in the latter group were obtained 5 to 7 times faster and the number of complications was greatly reduced. On the basis of their experience in the treatment of over 1000 cases of gonorrhea with sulfanilamide and related compounds Cokkinis and McElligott regarded sulfanilamide as "much the most efficient," its only drawback being its toxicity.

Most workers, even those disappointed in the results of the drug on local genital lesions, agreed that sulfanilamide therapy had sharply reduced gonorrheal complications (arthritis, etc.).<sup>610, 632, 638, 887</sup> The reduction was estimated to be more than 85 per cent by some (Cokkinis and McElligott), about 75 per cent by Alyea, Daniel and Harris, who noted practically no complications except among patients who had not received sulfanilamide. Previously about 42 per cent of gonorrheal patients had complications of one sort or another (Goldstein, cited by Alyea, Daniel and Harris). Alyea and his colleagues compiled the recent statistics of five workers who had treated with sulfanilamide 830 cases of gonorrhea, *in none of which complications developed*.

[It seems probable that regardless of whether the general incidence of genital gonorrhea is notably reduced or not, the incidence of gonorrheal arthritis will be markedly lowered as more and more patients begin early sulfanilamide therapy. Some physicians go so far as to prophesy that gonorrheal arthritis (which is regarded as affecting only about 3 per cent of patients with gonorrhea anyhow) may disappear. It is too early to make such a prediction, but some significance may be attached to the fact that, omitting the two reports which specifically and solely dealt with 23 cases of gonorrheal arthritis, we found mention of only an additional 31 cases of gonorrheal arthritis in a series of papers which concerned about 2247 cases of gonorrhea: instead of an incidence of 31 cases the expected incidence (at a rate of 3 per 100 cases) should have been 67 cases.—Ed.]

*Method of Administration of Sulfanilamide: General Comments.* In the matter of sulfanilamide therapy American physicians again exercised their rights to be individualistic; few of them followed the dosage-scheme proposed by the early workers in the field; they tried all manner of variations. But they<sup>128, 840</sup> generally subscribed to the following principles: in serious, potentially lethal diseases (e.g. puerperal sepsis,

meningococcal and serious hemolytic streptococcal infections) full doses were generally used, large initial doses, 120 to 180 grains daily until the desired concentration in blood was attained, and then reduction of dose. In such cases one group of physicians<sup>610</sup> gave one large initial single dose (100 grains or more), followed by high but smaller doses for 12 days only, and noted no serious toxicity. According to McGinty the largest published dose was that of Foulis and Barr (1937) given for puerperal sepsis: daily 215 grains for four days, 110 grains for three days; a total of 1190 grains (79.2 gm.) in seven days. [Bauer and Coggeshall gave a total of 1440 grains in 24 days to a patient with atrophic arthritis; the only toxic manifestation was cyanosis.—Ed.] For moderately severe diseases (e.g., gonorrhea) moderately high (80 to 120 grains daily) doses were first used, then a reduction when concentration in blood was adequate. For mild illnesses (e.g., urinary tract infections) small initial doses (30 to 40 grains daily for two or three days) were used and then the dose was increased. All the doses noted herein apply to adults unless otherwise stated. Jones<sup>500</sup> regarded the following plan as the accepted standard:

Oral Doses for 24 Hours, Grains

	Mild Infection	Severe Infection
Infants up to 40 pounds	15-25	30-50
Children 40-80 pounds	35-45	70-90
Older children 80-120 pounds	50-60	100-120
Adults	60-80	120-160

To obtain optimal results it is important to regard these points: 1. As early as possible one should produce as high a concentration of free sulfanilamide in blood as seems desirable for the disease under treatment and within the limits of a patient's tolerance. The early high dose should be continued until symptoms definitely improve (generally within three or four days) and the smaller maintenance doses should be continued (at least one or two weeks more) until a bacteriologic, not just a clinical, cure is obtained. *The continuing doses are of the greatest importance to prevent relapses and recurrences.* 2. Since maximal therapeutic effects often occur as early as the third or fourth day of medication the high initial doses are generally reduced about the fourth day. 3. To keep the concentration in blood about constant, doses should be given at evenly spaced intervals as far as possible both day and night. 4. For the same purpose the daily intake of fluid should be constant. (Differing daily amounts were allowed: 1200 to 1400 c.c.,<sup>128</sup> 1500 c.c.,<sup>610</sup> 2000 c.c.)<sup>24</sup>

*Scheme of Dosage for Gonorrhea and Gonorrheal Arthritis.* For the following reasons most physicians did not favor the use in gonorrhea of the large doses previously noted: 1. Gonorrhea is rarely lethal. 2. Most patients being treated are ambulatory. Although hospitalized patients can often tolerate 80 grains or more daily, ambulatory patients can rarely tolerate over 60 grains daily.<sup>430, 610</sup> 3. Experience shows that many gonorrheal patients are relieved of symptoms by rather moderate doses (40 to 50 grains daily).<sup>430</sup> Bannick, Brown and Foster noted that gonorrheal patients seemed to get good results with concentrations in blood of 5 to 7 mg. per cent and that concentrations of 10 mg. per cent were not required. Manor's results were the same in one group given moderately high doses (daily 70 grains for two days, 60 grains for three days, 20 grains for eight days) as in another group given low doses (22½ grains daily for 7 to 17 days). 4. The use of only

moderately high doses reduces the incidence of certain (but not all) complications and toxic reactions.

As an extra precaution to prevent toxic effects and control dosage some physicians gave no prescriptions for the drug, but dispensed from their offices the proper amount of pills for each dosage period, generally just enough for two to three days.<sup>185, 280</sup> Others gave prescriptions for just enough for each period of similar dosage, and stressed the importance of marking all prescriptions "No refill."<sup>873</sup>

Schemes of dosage for gonorrhea followed these general patterns: 1. Dosage was based on mathematical calculations to maintain concentrations in blood of 5 to 10 mg. per cent free sulfanilamide. Some workers based their dosage on a general plan of about 15 grains to every 20 pounds of body weight as the probable requirement to maintain the desired concentration.<sup>11, 500</sup> Calculating a tentative dose from the patient's weight but keeping their eyes on the concentration in the blood, they increased or reduced the dose as necessary to maintain the decreed concentration regardless of the patient's weight. To attain quickly and maintain the concentration desirable in gonorrhea Long recommended the following dose for (150 pound) adults: an initial single dose of 80 grains, then 20 grains every four hours for four or five days, then smaller doses given 10 days more to males, 25 days more to females. If there is no notable clinical response after the first four or five days, further sulfanilamide therapy probably will fail; other therapy should be used. Some<sup>185, 280</sup> criticized the use of these full doses as intolerable for most gonorrheal patients and likely to court complications.

[We cannot agree.—Ed.]

2. A "routine" dosage used which is not based on the patient's weight, consisted of a rather high early daily dosage (generally 80, rarely 120 grains), then a reduction. Having first used smaller doses in gonorrhea, Colston, Dees and Harrill (1937) later felt obliged to increase their daily dosage to 80 grains for two days, 60 grains for five days, 40 grains for seven days, 20 grains for 14 days. Mahoney, Van Slyke and Thayer<sup>610, 983</sup> considered the short use of large doses less toxic and more desirable than the longer use of small doses. They recommended for patients over 135 pounds, 120 grains daily for four to six days, then smaller doses for a total of only 12 days; for others they started with 80 grains daily for five to nine days. McGregor-Robertson also approved of the short use of large doses: 120 grains daily for three days, 96 grains for seven to eleven days. Others used full but slightly lower doses: Ellison, 80 grains daily for four days, 60 grains for three days, 40 grains for fourteen days, 20 grains for seven days; Cook and Buchtel, 75 grains daily for two to three days, 60 grains for two to three days, 40 grains for a total of fourteen days; then a rest period of ten to fourteen days, then *always* a second course to prevent recurrences; Vest, Harrill, Hill and Pitts, single first dose of 70 to 110 grains, then 60 to 100 grains daily; Aylea, Daniel and Harris, 90 grains for one day, 45 grains for thirteen days.

[To determine for himself how important the factor of dosage is the reader can note in table 1 the results obtained when these doses were used.—Ed.]

3. A routine scheme used (not based on patient's weight) consisted of moderate initial doses, then reduced doses. This scheme was followed by several.<sup>46, 49, 185, 438</sup> The highest doses given were generally 60, rarely 80 grains; thus Ballenger and his colleagues gave 60 to 80 grains daily for two or three days, 40 to 50 grains for five days, then smaller doses.

4. Another routine scheme consisted of a low or moderately low dosage which is unchanged. Unwilling to use larger doses because of toxicity Burns gave only 20 grains daily. Grodberg and Carey gave only 20 to 30 grains daily to women for four

to six weeks. 5. Early low or moderately low doses, later reduced even more, were given<sup>80, 130, 862</sup>; for example Butler gave 45 grains daily for four days, 25 for seven to ten days. 6. Early low doses were later increased.<sup>810</sup> Because of a "genuine respect" for the toxic properties of the drug, Harris first gave a "test dose" of 15 to 20 grains daily "for a certain period," thereafter no higher than 40 grains daily. 7. Combined oral and intramuscular administration of sulfanilamide has been suggested to maintain more readily its even concentration in the blood and it was used by Ainsworth. It satisfied the type of patient who likes "shots," the red color in urine had a good psychic effect, the need for injections brought patients regularly to the office and led to more careful and successful supervision. 8. Sulfanilamide therapy continued with other measures will be discussed later.

*Duration of Medication.* This also varied considerably, and the drug was given: only four days,<sup>574</sup> two to six days only,<sup>983</sup> four to six days only<sup>960</sup>; high doses, however, were given. It was given by others for eight days,<sup>688</sup> "not over ten days,"<sup>841</sup> ten to fourteen days,<sup>844</sup> twelve to fourteen days,<sup>185, 208, 485, 887</sup> "at least fourteen days,"<sup>11</sup> for twenty-one days,<sup>100, 458, 865</sup> "at least twenty-one days,"<sup>183</sup> not over twenty-one days regardless of the status of the disease,<sup>488</sup> twenty-eight days (moderate doses),<sup>453, 1043</sup> for four to six weeks (small doses).<sup>393</sup>

#### CONCLUSIONS AS TO THE PRESENT STATUS OF SULFANILAMIDE THERAPY FOR GONORRHEA AND GONORRHEAL ARTHRITIS

The *advantages* of sulfanilamide therapy for gonorrhea and its complications are many. The drug is easy and cheap to administer. It is essentially nontoxic, rarely producing serious reactions. It promptly cures genital gonorrhea and gonorrheal arthritis in about 70 per cent of cases even though it must often be given to ambulatory patients for whom dosage cannot be controlled satisfactorily. Its prompt use notably lessens the incidence of complications or generally controls rapidly those already present.

Its *disadvantages* are becoming more obvious. It occasionally provokes serious, even fatal toxic reactions; it very commonly produces reactions which, though mild, are quite annoying. Effective doses of it cannot be taken by 10 to 20 per cent of patients. By the methods so far used it has failed to cure about 30 per cent of patients with gonorrhea and an equal number of those with gonorrheal arthritis. Because it is so often effective clinically more rapidly than bacteriologically, it may lead to "false cures" when medication is stopped prematurely as is a constant danger. Its rational use demands careful prolonged bacteriologic diagnosis and control.

The attitude of urologists was summarized by Mathe and Spitalny from answers (number unstated) to questionnaires sent to 150 American and European urologists. On the basis of these replies it was judged that 90 per cent of the profession were using the drug; its distinct advantages (as noted previously) were fully recognized but it was considered quite toxic and its optimal dose difficult to establish (only one urologist advocated initial daily dose of 120 grains; the average daily doses used were 80 grains for two days, 50 grains for one day, 15 grains thereafter). Results therewith had not been as spectacular as originally reported, hence 85 per cent of the urologists replying regarded sulfanilamide merely as the most valuable *adjunct method* ever devised for gonorrhea, but one which should be more

or less routinely supplemented by additional therapy: generally local chemotherapy, occasionally supplemental fever therapy or vaccine therapy.

No final appraisal can be made without considerable further experience. Obviously much standardization is needed: standardization of the method of administration, the timing, dosage and duration of medication, and especially standardization as to the criteria of "cure."<sup>292</sup> At present the best criterion of cure is repeatedly negative *cultures* at suitable intervals; according to Long that should be the sole criterion. Some physicians already consider sulfanilamide for gonorrhea outdated by the use of sulfapyridine or other compounds. This remains to be proved; meanwhile these data on sulfanilamide will serve as a yardstick with which to measure the successes of other compounds.

### COMBINED THERAPY OF GONORRHEA: SULFANILAMIDE PLUS OTHER MEASURES

1. *Sulfanilamide Plus Local Chemotherapy.* Several physicians<sup>874, 439, 841, 865, 873, 899</sup> noted enough failures from the use of sulfanilamide alone for them to combine such therapy with orthodox local genito-urinary chemotherapy; many patients not cured by the first method were cured by the combination. To Sinkoe the main advantage of such combined therapy was that it compelled patients to return to his office frequently enough for close supervision and minimized the chief danger of unsupervised self-treatment, i.e., the cessation of treatment when symptoms improve before bacteriologic cure occurs. It is not surprising that Burns who only gave 20 grains of sulfanilamide daily, found it necessary to use local chemotherapy also. Ainsworth used combined oral and local therapy to obtain cures in 16 per cent of one series of 148 cases<sup>14</sup> and in 36 per cent of 230 other cases<sup>15</sup> in which sulfanilamide alone was ineffective. Others<sup>888</sup> recommended employment of additional local therapy "as if sulfanilamide were not being employed." According to Ballenger and his colleagues nearly all cases of early gonorrheal urethritis can be promptly cured by combining proper doses of sulfanilamide (early doses 60 to 80 grains) with the sealing (by collodion) of a 5 per cent solution of mild silver protein (argyrol) in the anterior urethra on four successive days: "This is surprising because a comparatively high percentage of failures occur when either procedure is used alone." They treated 79 consecutive patients by this method with only two failures.

[It is important to determine whether the combined method is actually superior because of the additional use of local treatment or simply because the sulfanilamide therapy was better controlled as a result of frequent office visits.—Ed.]

2. *Sulfanilamide Plus Vaccines.* For reasons noted previously Cokinis and McElligott delayed the use of sulfanilamide until after the eighth day of the infection, but "vaccine" injections were begun at the onset of infection and continued through the three weeks of sulfanilamide therapy in order to stimulate "enough immunity to dispose of the organisms arrested



by sulfanilamide." If necessary a second course was given by this method. "Total permanent cures in male patients can be increased to over 90 per cent."

3. *Sulfanilamide, Vaccine and Local Chemotherapy.* This combination was used by King in a few cases, also by Mathe who considered that the supplemental use of Corbus vaccine gave better results than when one remedy alone was used.

4. *Sulfanilamide with or Followed by Fever Therapy.* Several physicians stressed the curative value of sulfanilamide combined with or followed by fever therapy in the treatment of cases resistant to either method alone. Randall, Krusen and Bannick treated two groups of women with gonorrhea: cures were obtained in 29 (94 per cent) of 31 patients treated by fever therapy alone (one 10 hour session) and in 15 (94 per cent) of 16 patients given sulfanilamide alone. Thus each treatment failed to cure an equal percentage of cases. One patient resistant to sulfanilamide was promptly cured by fever and one resistant to fever was cured by the drug. Cures in gonorrhea can therefore be expected in almost all cases if one or both methods are used. Cook and Buchtel noted four gonorrheal cases resistant to sulfanilamide: three patients were cured by subsequent fever, and one with particularly resistant gonorrhea was cured by a combination of sulfanilamide plus fever (10 hours of general fever including 5 hours of supplementary pelvic heating). They recommended that cases of gonorrheal arthritis not notably relieved by three to six days of sulfanilamide should be promptly subjected to fever therapy. Elkins and Krusen cured by sulfanilamide two patients with gonorrheal arthritis resistant to the usually adequate amounts of fever, and cured by fever therapy nine of ten resistant to the drug alone. They prescribed 80 grains of the drug daily for two days prior to fever therapy (generally one 10 hour session at 106° F.). Eight cases of gonorrheal arthritis were successfully treated by Rock with fever plus sulfanilamide. One of Simmons and Dunn's patients with gonorrheal arthritis resistant to the drug alone was cured by the combined method: 40 grains of the drug daily for three days, then 10 hours of fever at 106° F. Atsatt prescribed 60 grains of the drug the day before a fever session (7 hours at 104 to 105° F.). Without giving details he stated that results from two or three such periods were more successful than from either alone, insuring "an almost perfect result." "Fascinating results" were noted by Ballenger, Elder, McDonald and Coleman who obtained by the combined methods "spectacular cures of stubborn cases" of gonorrhea unrelieved by either remedy alone. The drug (60 to 80 grains daily) was given for one to two days before the first fever session, and was continued between sessions of fever. Three fever sessions were generally given, one every other day. Of 31 patients with gonorrhea treated thus, 24 were cured within a week; 4 of them had gonorrheal arthritis. Some physicians suggested that when the combined method was used, smaller amounts of both fever and drug were effective. According to Wengatz, Boak and Carpenter

the thermal death time of gonococci at 41.5° C. was shortened by about 50 per cent when enough sulfanilamide was added so that blood broth cultures thereof contained a concentration of 10 mg. per cent. The fever sessions of Ballenger and his colleagues were only three hours at 104° F. Heald considered a fever of 102 to 104° F. by inductothermy adequate (detailed results and hours of fever unstated). However, Kendell (cited by Elkins and Krusen) and Elkins and Krusen found it necessary to use full, not abbreviated, fever sessions even when the drug was also used. To 11 patients with gonorrhea uncured by sulfanilamide, in "several" of whom arthritis had developed during medication (doses variable, some small, some moderately high), Owens, Wright and Lewis gave a conditioning fever treatment (three hours at 103 to 104° F.) and on the next day a full session (10 hours at 106 to 107° F.). Ten of the eleven patients were promptly cured clinically and bacteriologically. The other patient remained uncured but finally responded to subsequent sulfanilamide therapy (though previously resistant to it) as if the fever had made him more amenable to the drug.

Horowitz, however, deprecated the combined method because of the disturbing cyanosis he observed in three cases so treated: "If we add to the anoxia of fever therapy the additional danger of anoxia caused by sulfanilamide we are exposing our patients to a double hazard."

[This opinion, based on such a small experience, is contradicted by the larger experience of others.—Ed.]

#### TREATMENT OF GONORRHEA BY NEWER SULFONAMIDE COMPOUNDS

*Terminology 1.* Dimethylated disulfanilamide = sulfanilyl dimethyl sulfanilamide. Synonyms: Diseptal A; uleron; uliron; dimethyl-disulfanilamide.

*Terminology 2.* Monomethylated disulfanilamide = sulfanilyl monomethyl sulfanilamide. Synonym: Diseptal B.

*Terminology 3.* Nonmethylated disulfanilamide = sulfanilyl sulfanilamide. Synonyms: Diseptal C; disulon; disulfanilamide. The term "disulfanilamide" is restricted by some to mean the third compound (i.e., disulon or diseptal C); by others it is used to include any of the aforementioned disulfanilamide compounds; hence to them<sup>1031</sup> disulon, uliron and "sulfanilyl sulfanilamide" are all disulfanilamide.

*Terminology 4.* Soluseptasine = disodium para (gamma phenyl-propylamino) benzene sulfonamido-alpha-gamma-disulfonate.

*Terminology 5.* Sulfapyridine = 2-sulfanilamido pyridine or 2-p-aminobenzene-sulfonamido pyridine. Synonyms: M. and B. 693; dagenan.

1. *Uleron, Uliron, Dimethylated Disulfanilamide.* Some German workers consider this compound less toxic than sulfanilamide and curative in 75 to 88 per cent of cases of gonorrhea.<sup>346, 1027</sup>

Clinical results. Papers available for this review noted its effects in gonorrhea but only casually mentioned gonorrheal arthritis. In March 1938, O'Hanlon reported "promising results" with uleron in a few cases of gonorrhea resistant to sulfanilamide. In April O'Mally reviewed a few of the early German papers thereon, and noted his results in 22 cases of gonorrhea including an unstated number of cases of gonorrheal arthritis. The daily dosage was 6 to 8 "tablets" of "uliron" for four days, none for eight days and then a second course (total 20 to 32 gm.). The majority of patients "rapidly improved"; six were unimproved; two were lost sight of. O'Mally approved the German idea of delaying treatment during the first seven or ten days of disease and using adjunct local chemotherapy or vaccines.

Walsh gave "uleron" to 43 gonorrheal patients (none with arthritis): 22 were cured, 21 were not, probably because of the small doses used. However he recommended supplemental local irrigations. As with sulfanilamide there was with uleron the same tendency to early clinical, but delayed bacteriologic, cures. Without giving statistical results from uleron in 150 cases of gonorrhea (arthritis not mentioned) Cokkinis and McElligott stated their inability to agree with the optimism of German workers for this drug. Its ultimate effectiveness in gonorrhea seemed lower than that of sulfanilamide, and to obtain permanent cures several weeks of treatment were necessary. Treating a miscellaneous group of cases including gonorrhea, Bannick, Brown and Foster generally gave daily 60 grains, occasionally 105 grains; total doses varied from 120 grains within two or three days to 1440 grains in 25 days. Resulting blood concentrations averaged only 1.9 mg. per cent.

Toxicity. The drug was tolerated by some patients intolerant to sulfanilamide, and the general incidence of toxicity was low. A few patients noted the following: mild lassitude, headache, anorexia, nausea, malaise, mild cyanosis, skin rashes, vertigo, tinnitus.<sup>49, 724</sup> In one of Walsh's cases gastro-enteritis, fever and giant urticaria developed. Renal and hepatic damage occasionally occur,<sup>346</sup> and one death from uliron was reported in Germany.<sup>1031</sup> Slight methemoglobinemia was noted once but no change in blood cells, no reduction in the carbon dioxide combining power of plasma and no sulfhemoglobin.<sup>49</sup> Although the drug is therapeutically effective and produces few immediate toxic reactions its chief danger is the production of severe peripheral neuritis: five cases were noted by Cokkinis and McElligott, two by Bannick, Brown and Foster, 1 by Van Valkenburg and Von dem Borne, 1 by Wigton and Johnson and eight in Germany.<sup>1031</sup> The drug will produce severe peripheral neuritis in pigeons also.<sup>1031</sup> Hence this drug is no longer used by several workers (Bannick, Brown, Foster; Whitby).

2. *Disseptal B*. No clinical reports with this compound were noted.

3. *Disulon, Diseptal C, Sulfanilyl Sulfanilamide, Disulfanilamide*. Two patients with gonorrhea (no arthritis) stubbornly resistant to sulfanilamide were cured by disulfanilamide (Alyea, Daniel and Harris). Disulfanilamide is absorbed more slowly but excreted more rapidly than sulfanilamide;

ethanol sulfanilamide is absorbed and excreted better than either (Marshall, Cutting and Cover). Wigton and Johnson reported three cases of severe peripheral neuritis from "disulon" and "sulfanilyl sulfanilamide."

4. *Soluseptasine*. O'Hanlon noted no beneficial effect from this drug in cases of gonorrhea resistant to sulfanilamide.

5. *Sulfapyridine, 2-Sulfanilamido Pyridine M and B 693*. Results with this drug in gonorrhea are, according to Lloyd, Erskine and Johnson, markedly superior to those with sulfanilamide or other sulfonamide compounds. They treated 108 patients with acute gonorrhea (arthritis not mentioned). There were 28 "defaulters." Of the 80 who completed the course of treatment results were "successful" in 85 per cent. Among those cured were some who had gonorrhea resistant to sulfanilamide.

[Results were somewhat difficult to evaluate because some patients were also treated by irrigations.—Ed.]

To 30 patients with genital gonorrhea, six of whom had gonorrhea resistant to sulfanilamide, Bowie gave sulfapyridine daily 45 grains for four to seven days, 20 grains for four to seven days. All patients were bacteriologically cured within one to seventeen days. The drug was considered more rapidly effective than sulfanilamide or benzyl sulfanilamide. Prebble gave sulfapyridine alone (45 grains daily for 5 to 12 days) to 25 gonorrheal patients: 48 per cent were cured, 52 per cent were not. He gave the drug and irrigations to 40 other patients: 63 per cent were cured, 37 per cent were not. Combined therapy was obviously superior (apparently arthritis was not present). Batchelor and his colleagues obtained "over 91 per cent apparent cures" among 102 gonorrheal patients (joints unmentioned) given an average daily dose of 30 to 45 grains for five to six days, then 20 to 30 grains for seven days. Males were cured within seven days, females within fourteen days. Early, not "delayed therapy" was advised.

[These papers give no definite idea of the value of the drug in gonorrheal arthritis. In general the follow-up periods were short.—Ed.]

Toxicity. From experiments on rats, mice and dogs Wien concluded that sulfapyridine is only a fourth as toxic as sulfanilamide. But Marshall, Bratton and Litchfield criticized Wien's work since it was based on the oral administration of poorly absorbed suspensions. From studies based on concentrations in blood they found the drug actually more toxic than sulfanilamide and stated that it should not be used in conditions in which sulfanilamide is generally effective. Toxic reactions were noted in 6,<sup>74</sup> 23<sup>107</sup> and 29 per cent<sup>55</sup> of patients so treated. They were generally mild, rarely serious (nausea, vomiting, diarrhea, skin rashes, cyanosis, headache, vertigo, methemoglobinemia, fainting, depression, urobilinuria, slight granulocytopenia, and in two cases jaundice). Prebble considered it slightly more toxic than uleron but more effective in gonorrhea. Sulfapyridine is used in smaller doses than sulfanilamide: in comparable doses both are probably equally toxic for man (Lloyd, Erskine and Johnson).

## OLDER REMEDIES FOR GONORRHEA AND GONORRHEAL ARTHRITIS

The following remedies appear to be completely outmoded but some physicians will wish to compare their results with those from the newer remedies. Of Spink and Keefer's 70 cases of gonorrheal arthritis 26 were treated by "medical means" (local chemotherapy, physical therapy, sometimes triple typhoid or gonococcus vaccine): in 20 (77 per cent) of these 26 cases full articular function was restored. Two patients died: one from acute glomerulonephritis, one from pneumonia. In 24 of the 70 cases aspiration of (generally sterile) articular effusions was also "required": normal function of the joints was obtained in 14 (48 per cent). In the remaining 20 cases aspiration of purulent, generally infected, synovial exudates was also required: in only 3 (15 per cent) was complete articular function restored.

Intra-articular injections of rivanol (ethyl oxy-diamino-acridinium hydrochloride) were advocated by Burbacher and Weiland. According to them "acute symptoms are aborted in 60 per cent of acute cases within 48 hours; relief of symptoms is noted in 95 to 98 per cent of all acute cases," generally after only one injection.

[Only one case was reported in detail: data given were insufficient to prove the conclusion to the reader.—Ed.]

*For Nonarticular Gonorrhea; Vaccines, Filtrates, Serums, Hormones.* Corbus restated the supposed rationale for the serologic control of gonorrheal infections by means of the bouillon filtrate (Corbus-Ferry). Of 24 cases of juvenile vaginitis so treated Goldberg and Blanchard noted cures in 54 per cent. But Scarcello found that such treatment took almost three times as long to produce satisfactory results as sulfanilamide. In Kushner's 36 cases of vaginitis treated by this filtrate it took an average of seven weeks to obtain the first negative smears. Results were "good" in 47 per cent, poor in 53 per cent. Others<sup>180</sup> spoke of the filtrate as having "failed miserably as a cure." Sherman considered a special "antivirus" of value. "Clinical cures" were obtained by 63 per cent of 247 gonorrheal patients given a mixed "antivirus" obtained from broth cultures of mixed organisms found in gonorrheal urethritis; by 44 per cent of 109 patients given a pure "antivirus," and by 67 per cent of 94 patients treated only with local chemotherapy. In the first two groups cures were obtained more rapidly and there were fewer complications than in the last group.

In 1937 Anwyl-Davies reported excellent results in cases of gonorrhea treated by a serum described as a "specific gonococcal antitoxin." The results of others have been very poor. Of 129 cases treated by Burke, Gabe, Harkness and King results were only "fair" in 13 per cent, bad in 87 per cent. Untoward reactions affected 41 per cent, complications, 21 per cent of patients so treated. Use of the serum was considered inadvisable, probably detrimental.

One physician<sup>502</sup> attempted active immunization of women with chronic pelvic gonorrhea by cultures of living gonococcus: 49 (77 per cent) of 63 patients were thus cured. According to Verdier hydrochloric acid is a component part of leukocytes, and when injected intravenously it stimulates and "reinforces" leukocytic activity. He and his associates have given to gonorrheal patients "many thousand injections" generally intravenously, occasionally intramuscularly (each injection 10 c.c. in a dilution of 1:500 HCl). "In no case has there been a failure to achieve curative results. Moreover, there has never been an unfavorable reaction." Brief reports of 25 cases treated by this "new and revolutionary" method were given; "cures" were obtained in every case after four weeks to four months of treatment.

[This report seems very unconvincing to us. The time was long enough for many "cures" to occur spontaneously.—Ed.]

The results of Te Linde in the treatment of juvenile gonococcal vaginitis by estrogenic hormone were excellent. When amniotin was given by mouth or subcutane-

ously in ethylene glycol results were very poor. But cures were obtained in 72 per cent of cases when estrogen in oil was given hypodermically, and in practically 100 per cent of 175 cases when vaginal suppositories (600 international units) of amniotin were given. Good results were also noted by Benson.

### TUBERCULOUS ARTHRITIS: GENERAL COMMENTS

*Clinical Data.* The course of tuberculous arthritis can be divided, according to Whitaker, into four phases: 1. During the *period of onset* a tuberculous focus develops in articular bone; this focus may or may not be preceded by one in synovial tissue. 2. During the *destructive phase* articular dissolution tends to occur, general decalcification is always present, and abscesses are sometimes seen. Eventually destruction ceases and the next phase begins imperceptibly. 3. The *quiescent phase* is not characterized by any particular clinical signs. 4. The *period of repair* is characterized by increased bony density, calcification of any bony abscesses present and subsequent bony ankylosis.

[Ankylosis rarely occurs unless the joint is secondarily infected. One of us, A. J. K., has not seen it in a proved case of tuberculous arthritis except in the spine.—Ed.]

*Diagnosis.* The diagnosis rests chiefly on the development of rather characteristic clinical and roentgenographic features, the latter being more important than the former.<sup>650</sup> Some physicians considered the various accessory skin and conjunctival tests of doubtful value<sup>650</sup>; others considered them useful. In all of the cases finally accepted by Whitaker as tuberculous results of Mantoux tests were positive. A standardized technic is important: negative results are more significant than positive; a condition associated with a repeatedly negative result is nontuberculous. Removal of a piece of articular bone or synovial tissue, examination thereof by microscopy and injection into guinea pigs still remain the only strictly accurate method for early diagnosis. But its routine application to hip joints was abandoned by McMurray because of the risk of permanent sinuses.

*Treatment.* Prophylactic therapy is of the greatest importance. In Australia most cases are caused by human, not bovine, strains of tubercle bacilli. A definite contact between the patient and a person with open pulmonary tuberculosis was established in 50 per cent of Whitaker's cases. In infantile tuberculous arthritis contact was almost always between the infant and a "parent just home from a sanatorium." Such contacts must be prevented by public health authorities.

Since tuberculous arthritis is merely a local manifestation of a constitutional disease its treatment must be (1) constitutional and (2) local. Fundamental features of constitutional therapy include rest, fresh air, sunlight, diet therapy, and removal of septic foci.<sup>204, 205</sup> Artificial stimulation of bodily resistance was considered valueless (Whitaker). According to Colvin, adequate constitutional treatment cannot be obtained in general hos-

pitals, but only at special open-air hospitals where proper constitutional and local therapy can be combined. Recently physicians have expressed a growing conservatism as to whether the most successful local therapy involves use of surgical or nonsurgical procedures. Current reports again indicate an increased appreciation of the value of conservative, i.e., nonsurgical, methods.

Cases of tuberculous arthritis at any stage were not considered suitable for hydrologic spa therapy,<sup>954</sup> or for synovectomy.<sup>482</sup>

### TUBERCULOUS ARTHRITIS; SPECIAL LOCALIZATIONS

Tuberculous arthritis more commonly affects lower extremities of children, upper extremities of adults. Involvement of upper extremities is about seven to nine times less common than that of lower extremities but is more severe and destructive (Steindler).

*Shoulder.* Tuberculous arthritis of a shoulder is rare; it affects adults (generally aged 40 to 50 years) four times as often as children. The synovial bursa of the biceps is a common primary source of infection. Steindler recognized two types: (1) a fungus synovial type present in 25 per cent of cases and (2) a primary osseous type. The latter was subdivided into (*a*) caries sicca and (*b*) fungus osseous type. The caries sicca type of tuberculous arthritis was the more common, and was characterized by dry destruction of cartilage and subchondral bone, atrophy of adjacent muscles, no articular swelling, a tendency to slow spontaneous fibrous ankylosis. Because of the last, end results were more favorable. The fungus osseous type was associated with granulomatous proliferation, marked swelling, abscesses (in a third of cases) and sinus formation. Its treatment is more difficult. Incision and drainage of abscesses give only temporary improvement. Resection is indicated occasionally, but operative fusion is generally necessary (with the arm in position of about 30 to 50 degrees abduction and forward flexion), and usually results in solid fusion of a painless joint with a fair range of motion of the shoulder at acromioclavicular and sternoclavicular joints.

*Elbow.* Tuberculosis of this joint is not uncommon and affects two adults to one child. Steindler recognized types and subtypes as in tuberculosis of shoulders, and noted abscesses in a third of his cases. Healing with full mobility occasionally occurred, more often in children than in adults; hence conservative treatment (long immobilization until the disease becomes inactive, then mobilization) is more applicable to the former. Surgical treatment is generally necessary. Arthrotomy is usually inadequate. Fairly early fusion of the joint in a suitable position gives best results.<sup>909</sup>

*Wrist.* This joint is affected more often than shoulders, less often than elbows, more often in adults than children. It is commonly associated with tuberculosis of adjacent flexor tendons and of lungs. Surgical therapy is indicated if roentgenograms indicate progression of the disease after two

or three months' immobilization of the wrist in a plaster splint. Total resection was considered superior to partial resection. Incision and drainage were considered useless, amputation rarely indicated.

[By some, early arthrodesis is considered the best.—Ed.]

In tuberculosis of joints of upper extremities, Steindler considered results of surgical treatment superior to those of conservative therapy.

*Knee.* In treating tuberculous arthritis of a knee joint by arthrodesis the patella offers a practical source from which a bone graft may be obtained. Meng described a new method for this procedure.

*Spine.* A careful "unprejudiced" 10 year test was made by Finkelstein, Greenberg, Jahss and Mayer to determine the relative value of surgical and conservative treatment of tuberculous spondylitis, to answer specifically the question: "Does the [fusion] operation shorten the course of the disease and prevent deformity?" One group of 26 patients was treated by fusion (Kleinberg method once, Hibbs method three times, otherwise the Albee method). The other group (17 patients) received "purely conservative measures" (complete rest on frames or plaster shells, the best of food, sunlight, fresh air, and in a few cases special measures such as tuberculin therapy, liver meal, splenic extracts, etc.). The two groups were closely parallel as to age of patients, duration, severity and location of disease. Strict criteria of "cure" were laid down. The surgical group required 40 per cent *more* time (average 1215 days) for their cure than the nonsurgical group (average 876 days). Apparently fusion operations prolonged, rather than shortened, the course of the disease. Despite firm fusions the pathologic process in the vertebrae themselves was apparently uninfluenced. Abscesses developed in 20 per cent of the surgical, in 18 per cent of the other group. Operation did not prevent paraplegia which occurred in four cases of each group. In spite of "successful fusion" recurrences occurred. Spinal deformity appeared to progress equally in both groups.

In conclusion the investigators were "impressed not only by the ineffectiveness of the fusion operation but by our ineffectiveness as physicians. An average of 876 days of care for patients not operated on is a high figure" which confirms experiences of others and shows how little can be done to hasten healing. "We are compelled to admit that tuberculosis of the spine is a chronic disease which runs its course, little influenced by the efforts of the orthopedic surgeon. This should act as an incentive to the development of more effective methods of treatment."

[These results are contrary to the experience of one of us, A. J. K. Further studies on this problem are needed.—Ed.]

*Hips.* Location of the primary articular tuberculous focus in 82 cases of tuberculous hips was noted by Hatcher and Phemister. The disease began in childhood in 70 cases, in adult life in 12 cases. Of children, the primary focus was in the neck of the femur in 14 cases, in the ilium in 10, in the ischium in 2, unlocated in 44. In no case was it in the head (epiphysis) of the femur. In other hematogenous infections also the femoral



capital epiphysis seems to be immune as a site of primary focus; this immunity seems to be dependent on the blood supply of the femoral head. The primary focus of the 12 adults was in a greater trochanter in two cases, in the ilium in one, unlocated in nine.

Tuberculous hips are uncommon in Australia, especially in South Australia where there have been less than 100 cases in 20 years (Betts).

Details of treatment were reviewed (Betts; Colvin; McMurray; Whitaker). The essence of treatment is complete, uninterrupted, prolonged fixation of the joint by surgical or nonsurgical means, fixation being continued until the disease becomes clinically and roentgenographically inactive. Articular destruction results chiefly from increased intra-articular pressure due to weight bearing and muscle spasm. [Is not articular destruction due to erosion of bone by tuberculous granulation tissue?—Ed.] These factors can be corrected by treating the patient in recumbency and relaxing muscle spasm by complete articular fixation. The method of fixation chosen may vary. Current writers unanimously favored prolonged trial of nonsurgical methods and the use of surgical operations only late in the disease when conservative therapy had failed definitely.

[One of us still believes that early surgical fusion of tuberculous hips is generally indicated.—Ed.]

For nonsurgical fixation the splint or frame used must be rigid enough to fix the joint but must permit access of sun and air to the joint, application of dressings to sinuses, and general nursing care without alteration of the joint's position. During the period of treatment in recumbency use of a Jones abduction frame was favored by Betts, Colvin, and McMurray; a bivalved plaster spica with subsequent use of a Bradford frame was favored by Whitaker. Colvin also used traction. Time required for treatment in recumbency varied from 1.5 to 2 or 3 years in McMurray's cases. Evidences of inactivity of the disease are absence of fever, pain and formation of abscesses, improved general health, and bony recalcification.<sup>650</sup> When the disease becomes inactive ambulatory therapy is indicated. Fibrous ankylosis generally results unless secondary infection occurs, in which case bony ankylosis may ensue. If the latter occurs, no external support may be necessary during "ambulatory treatment." Otherwise some external support is generally required unless the presence of short, stout, wide, fibrous ankylosis has produced as "sound" an ankylosis as a bony one. Some physicians used plaster, a leather case or single Thomas splint<sup>650</sup>; others used a walking spica or a double Thomas splint.<sup>82, 1025</sup> Such conservative ambulatory treatment should be continued for at least 18 months. If a sound ankylosis has not occurred, then and only then should surgical methods be considered. The likelihood of a sound or unsound ankylosis can be predicted by certain roentgenographic features.<sup>650</sup> Conservative therapy has been reported to produce sound ankylosis in hips in "at least 70 per cent of patients,"<sup>650</sup> and in "the majority" of cases.<sup>82, 204</sup>

The following results from conservative therapy were noted. In Col-

vin's series successful results were obtained in 21 per cent of cases with sinuses antedating treatment, and in 58 per cent of those without sinuses. Sound ankylosis resulted in 22 of Betts' 31 cases. Whitaker obtained bony ankylosis in 40 per cent, "presumptive ankylosis" in 55 per cent, no ankylosis in 5 per cent. The disease lasted an average of at least five or six years. Disadvantages of conservative therapy are that it is costly in time and money and is occasionally ineffective.

[Unfortunately some tuberculous hips "soundly ankylosed" by fibrous tissue flare up later and require arthrodesis.—Ed.]

Surgical procedures in vogue are (1) intra-articular arthrodesis ("generally unsatisfactory")<sup>650</sup>; (2) extra-articular arthrodesis; "more satisfactory"; (3) the combined method (preferred by McMurray); (4) production of a pseudarthrosis (valuable for elderly patients); (5) corrective operations, e.g., various forms of osteotomy (preferred by Betts). There is no urgency in the matter of surgery.<sup>204</sup> Sometimes a "successful" early fusion operation may be actually harmful by retarding collapse and closure of the bony cavity produced by osseous destruction. Disadvantages of surgical therapy are that there are definite chances for death therefrom or for secondary infection, sinus formation or unsuccessful fixation thereafter. "Operation does not help to control or diminish joint dissolution" (Whitaker).

[In this some of us do not agree.—Ed.]

### TUBERCULOUS RHEUMATISM

According to Najib-Farah genuine acute rheumatism (i.e., rheumatic fever) and Poncet's tuberculous rheumatism are often mistaken for each other. In five "typical cases" of Poncet's rheumatism the plasma bilirubin concentrations varied between 0.1 and 0.3 mg. per cent; in "genuine acute rheumatism" the concentrations were always higher, a point of diagnostic significance.

[These are very low figures for plasma bilirubin; the method used for their estimation was not stated. No clinical data were given to clarify the supposed entity of tuberculous rheumatism, one not accepted in the United States.—Ed.]

### PNEUMOCOCCAL ARTHRITIS

Pneumococcal arthritis is rare,<sup>5</sup> and will probably become rarer if the promising results from use of the newer sulfonamide compounds are confirmed. No cases of pneumococcal arthritis were noted among the numerous cases of pneumococcal infections treated recently with sulfanilamide or sulfapyridine.

Earlier reports<sup>5</sup> indicated that sulfanilamide had slight but definite pneumococcal properties. In some cases the drug favorably affected experimental pneumonia (types I and III), human pneumonia (especially type III), pneumococcal meningitis and brain abscess (type V), septicemia (type II), and otitis media (type III). But in other instances similar conditions were not benefited. Further results with sulf-

anilamide have been generally disappointing. Beneficial effects have been ascribed to the drug in the treatment of experimental pneumonia (types III and VII),<sup>209</sup> experimental pneumococcic meningitis (types I and III),<sup>544</sup> human pneumonia (types I to IX)<sup>116, 737, 704, 824, 1036</sup>; but especially in treatment of the usually fatal pneumococcic meningitis. Recovery in 14 cases of the last disease (from various types of pneumococci) was reported.<sup>21, 38, 313, 1055</sup> Some physicians noted no effect in other cases of pneumonia<sup>116</sup> and pneumococcic meningitis.<sup>913</sup> Long and his colleagues<sup>298</sup> considered sulfanilamide of little value in pneumococcic pneumonia but somewhat effective in type IV pneumococcic meningitis. Osgood<sup>737</sup> noted that the drug had a slight inhibitory effect on pneumococci (types I, II, III and VIII) in human bone marrow cultures but not as much as small doses of serum. Sulfanilamide and serum combined had an effect superior to either alone. No justification was found for the use of sulfanilamide alone in human pneumonia. The effects of disulon, uleron, and septasine on experimental pneumonia (types I and III) in mice were insignificant; that of diamino diphenylsulfone was very definite but the drug is too toxic for humans.<sup>298</sup>

Much more striking have been the effects of sulfapyridine. Whitby showed that the drug possessed great activity against pneumococci and experimental pneumococcic infections of several types, especially types I, VII and VIII, less notably types II, III and V. Rapid recovery following use of the drug was noted in many cases of lobar pneumonia from various types of pneumococci,<sup>260, 291, 822, 947</sup> and in pneumococcic meningitis<sup>797</sup> and septicemia.<sup>259</sup> Evans and Gaisford noted a reduction of mortality from 27 per cent of 100 cases of pneumonia treated otherwise to 8 per cent of 100 cases treated with sulfapyridine. The drug causes degeneration of the capsule of the pneumococci and resulting loss of their type specificity.

#### SYPHILITIC ARTHRITIS AND SYNOVITIS: CHARCOT (TABETIC) JOINTS

The various ways in which syphilis may affect muscles, joints and related structures were briefly reviewed and the commoner types were discussed in some detail.<sup>640, 701, 703, 879</sup>

1. *Arthralgia*. This affects 5 to 10 per cent of patients with early syphilis. Pain arises from an unknown cause, perhaps from mild juxta-articular periostitis. Among 8000 consecutive cases of syphilis studied by New and Brittingham were 61 (0.76 per cent) of "inflammation of joints." Pain affected one joint in 7 cases, multiple joints in 54 cases, and was quickly relieved by two or three injections of neoarsphenamine. Severe joint pain was present but no bony changes, no case of Charcot joint and only one case with hydrops (knee). "Whether such *inflammation* is a true arthritis or merely an arthralgia is not important."

[We cannot agree to this statement. Not enough details were given for one to conclude what type of articular disease was present.—Ed.]

2. *Syphilitic Synovitis or Arthritis*. This occurs in only 1 per cent of cases of early syphilis, more often in late syphilis. The commonest variety is "Clutton's joint," bilateral synovitis with hydrops of knees in a congenital syphilitic. It is characterized by marked swelling, slight heat, pain and tenderness, no redness and no bony changes even though the condition may persist for years. The cellular content of synovial fluid is not characteristic; total synovial leukocytes number 10,000 to 45,000, and relative lymphocytosis is present (McEwen and Thomas).

Synovitis may also affect patients with acquired syphilis. Synovectomy was considered very useful (Swett).

[To us synovectomy in such cases seems unwise and unnecessary since antisyphilitic treatment is generally promptly effective.—Ed.]

Syphilitic polyarthritis may occasionally occur.<sup>640</sup> Diagnosis is based on the clinical features, lack of response to antirheumatic measures, positive Wassermann reaction, and prompt response to antisyphilitic therapy.

3. *Gummatous Arthritis*. This occurs only in tertiary syphilis. Roentgenograms may reveal large or small gummatous areas of destruction and sometimes secondary osteo-arthritis. An illustrative case was described.<sup>640</sup> According to Smith<sup>879</sup> this type "may often assume the characteristics of rheumatoid arthritis with fusiform swelling of fingers, pain, intermittent temperature with exacerbations and remissions. It may so closely resemble chronic rheumatoid arthritis as to justify serological study of all cases so diagnosed." But McEwen and Thomas never saw a case of syphilitic arthritis in which differentiation from rheumatoid arthritis was difficult.

[Our experience coincides with that of McEwen and Thomas. Nonarticular syphilis and atrophic arthritis may occasionally coexist.—Ed.]

4. *Periostitis Adjacent to Joints*. This may cause arthralgia. An illustrative case was described.<sup>640</sup>

5. *Charcot Joint, Tabetic Osteo-Arthropathy*. This affects about 4 per cent of tabetics; in 75 per cent of cases joints of lower extremities are affected. The usual features were described: slow or sudden onset of articular swelling and instability, effusions present or absent, variable degrees of joint destruction, characteristic roentgenographic and neurologic abnormalities. [The joints are generally painless, occasionally even anesthetic, but sometimes somewhat painful.—Ed.] The condition may progress slowly or rapidly. Its exact pathogenesis is unknown. Seven new cases were reported.<sup>181, 640, 658, 792, 1050</sup> That of Menninger and Carlson was very unusual: a case of congenital syphilis in a 60 year old woman who at the age of 43 years began to develop multiple tabetic arthropathies (a hip, a lumbar vertebra).

The treatment of Charcot joints is usually unsatisfactory. Antisyphilitic therapy is not effective. Mechanical supports are generally prescribed. McEwen and Thomas reported some success with fusion operations in cases with little articular destruction. Operation too often fails to provide a stiff joint. An improved technic for arthrodesis of Charcot joints was described by Soto-Hall: multiple bone drillings of involved articular bones to improve vascularity and osteogenesis; immobilization for four to six weeks by a posterior plaster splint; then a standard arthrodesis.

[This appears to be a procedure worthy of more extended trial.—Ed.]

Fever therapy does not affect Charcot joints but may be a prophylactic measure as it may favorably affect cases of early or late neurosyphilis. Several references will interest those concerned with the present status of fever therapy for syphilis.<sup>72, 74, 474, 647, 709, 735, 751, 837, 885</sup>

6. *Rarer Forms.* Some rarer, less certain forms of supposed syphilitic rheumatism were noted,<sup>879</sup> including that of a young woman with severe syphilitic osteolytic lesions of bones, especially radius and ulna, severe tenderness and pain in muscles, bones and joints, and extreme muscle atrophy; antisyphilitic treatment rapidly relieved the symptoms (Newman and Saunders).

### BRUCELLOSIS, UNDULANT (MALTA) FEVER

*Incidence.* From 1930 to 1937 inclusive 14,938 cases of brucellosis with 597 deaths therefrom were reported in the United States (2,497 cases with 58 deaths in 1937). Yearly figures were reported for each state. "The total number of cases actually occurring is undoubtedly much larger than that reported." These totals, published by the United States Public Health Service<sup>976</sup> are slightly higher than the unofficial totals collected by physicians and reported in previous Reviews. Studies on the incidence of the disease were also reported from Connecticut,<sup>957</sup> Pennsylvania,<sup>320, 321</sup> Vancouver,<sup>251</sup> England,<sup>235</sup> Scotland,<sup>61, 62</sup> Malta,<sup>349</sup> and Egypt.<sup>61, 537, 1050</sup>

*Clinical Data.* Several short general reviews of the subject appeared.<sup>164, 235, 289, 748</sup> The incubation period of the disease varies from one week to not less than four months (Hardy, Frant and Kroll). The new cases illustrated again the protean symptoms of the disease. Commonest symptoms were fever of varying severity and duration, chilliness, fatigue, weakness, sweating, malaise, headache and generalized aching. Any of these symptoms can be dominant, with others slight or absent. Leukopenia generally is present, occasionally leukocytosis, with relative monocytosis. Because of the vague general symptoms the disease, when acute, is commonly misdiagnosed as influenza, or when chronic, neurasthenia or tuberculosis. Sometimes the disease produces more discrete symptoms: pneumonia, meningitis, iritis.<sup>94, 705</sup> Postmortem studies are of interest because they are rare: those in two cases were reported.<sup>94, 655</sup>

*Symptoms Referable to Muscles and Joints.* As previously, certain writers<sup>369, 370, 946, 795</sup> have again stressed the frequency of actual arthritis (acute or chronic) as a common feature of brucellosis, but a careful review of current reports leads to the conclusion that a true arthritis rarely occurs although arthralgia and myalgia are common symptoms. Of the Abbotts' 11 patients seven had general aching, backache and neckache and one "extreme joint pains." Two authorities (Evans<sup>289</sup>; Dalrymple-Champneys) noted "joint pains" and "pains in limbs" not infrequently but did not mention true arthritis as a feature. Patients with "pains in back and joints,"<sup>343</sup> "muscle and joint pains,"<sup>251, 655</sup> "cramp-like pains in muscles of arms and legs,"<sup>777</sup> "severe joint pains" (in one of 28 cases),<sup>200</sup> "sciatica" (in one of 20 cases),<sup>708</sup> and "rheumatic pains in joints"<sup>707, 708</sup> were noted. But these were not constant features and many patients apparently experienced no joint or muscle pains.<sup>320, 321, 749</sup> A previous diagnosis of "rheumatic fever" in one case and "septic arthritis" in another became obviously un-

tenable to Dolman. Arthritis was a major complaint in 12 of the 100 cases of Schmidt and Dorsey (Oklahoma). In a few of the cases of Passarelli and Sloan "inflammatory joints" were noted: "General muscle and joint pains are common, and joint involvement resembling that of rheumatic fever is not uncommon." But they are not definitely responsive to salicylates. Newman<sup>705, 707</sup> himself had "probable undulant fever"; for the next 20 years he suffered periodically from attacks of muscle, joint and nerve pain which affected a sciatic nerve, a shoulder, sometimes many joints. Attacks of pain and stiffness recurred for two to three days every three to four weeks, were unrelieved by removal of foci, but relieved when at long last treatment for brucellosis was begun. "If the physician will round up his chronic complainers and neurotics, especially those complaining of neuralgia and arthralgia, and apply modern methods of diagnosis he will be shocked to find how many really have the disease [brucellosis]." <sup>707</sup>

[In some such cases of myalgia, arthralgia and fatigue a diagnosis of "primary fibrositis" might be entertained, but the differentiation should not be difficult. In primary fibrositis there is no fever, no characteristic leukopenia, and the sedimentation rate is practically always normal. In brucellosis there is usually some fever and sedimentation rates are generally abnormal.—Ed.]

That brucellosis commonly masquerades as chronic atrophic arthritis is the idea again expressed by a few physicians in the Southwest. Thus McIntire (Texas) wrote: "Brucellosis is one of the many causes of chronic arthritis. Two patients reported who had rather extensive atrophic arthritis with complicating hypertrophic changes. Both patients had strongly positive tests for brucellosis; both were extremely sensitive to the intracutaneous test." [It is likely the arthritis was quite unrelated to the brucellosis. No evidence was given that the arthritis responded to antibrucellosis therapy.—Ed.] Reed and Goldfain noted five patients with recurrent iritis, three of whom had rheumatic symptoms, the syndrome being due presumably to brucellosis. [Iritis sometimes complicates cases of atrophic arthritis.—Ed.] One patient had "Marie-Strumpell spondylitis" with irritation of an eyeball recurring "since he began to have his serious symptoms of arthritis." Another patient had recurrent lumbago and iritis; a skin test for brucellosis provoked both complaints. Another patient had muscle and joint aches, fever, malaise and iritis, later "subacute synovitis" of a knee and ankle. In all these cases laboratory tests indicated the presence of brucellosis. In the last case the arthritic symptoms disappeared, once under nonspecific therapy, later after specific vaccine therapy for brucellosis.

Fifty cases of "apparent rheumatic and arthritic disease" were tested by Goldfain<sup>370</sup> (Oklahoma) for brucellosis. [The terms "rheumatic and arthritic" seem to have been used rather liberally as among the 50 cases there were six of "psychasthenia" or "psychoneurosis" and one of "chronic choroiditis." These are not "rheumatic diseases." There were 19 of "atrophic arthritis," 10 of "hypertrophic arthritis," 8 of "fibrositis," 3 of "psychoneurosis or psychasthenia and fibrositis," 2 of "sciatica," one of "ankylosing spondylitis."—Ed.] Fourteen patients gave "positive agglutination tests" (titers unstated); 36 had positive

reactions to skin tests of mild to severe degree; mild to marked opsonophagocytic activity of blood was present in all cases. It was concluded that 31 of these patients with apparent rheumatism actually had "active brucellosis in addition to other diagnoses." Arthralgia was present in all 31 cases, backache in 90 per cent, neuritis and neuralgia in 48 per cent, myositis in 32 per cent, spondylitis in 6 per cent, "persistent joint stiffness" in 26 per cent. It was inferred that these symptoms were expressions of the brucellosis. In another group of 157 patients "the great preponderance of whom were suffering with rheumatic disease" (apparently 80) 51 per cent were given a diagnosis of brucellosis by Goldfain<sup>369</sup> on the basis of similar laboratory tests. Of 23 patients adequately treated with *Brucella* bacterin 90 per cent were improved or cured. Admittedly results may have been due to non-specific protein therapy.

[These reports have failed to prove that the rheumatic symptoms were actually due to brucellosis, or for that matter, that active clinical brucellosis was present. Apparently in the Southwest, especially Oklahoma, latent brucellosis is quite common. Perhaps a similar number of patients with any chronic disease might show a similar percentage with "positive" results to tests for brucellosis. Either the Oklahoma strains of *Brucella* are peculiarly arthrotropic or these cases represent the coincidental relationship of chronic rheumatism and latent (unrelated) brucellosis. In the light of most reports we are not convinced that true acute or chronic arthritis is commonly due to brucellosis. Previous Reviews have noted rare bona fide cases of specific joint and muscle lesions from brucellosis.—Ed.]

*Diagnosis.* The significance of laboratory methods used to confirm the clinical diagnosis was again discussed. Opinions differed as to which of several tests is the most reliable.

*Agglutination Tests.* In the University of Pennsylvania Hospital and in the Cook County Hospital, Chicago, a titer of 1:80 or over is considered positive.<sup>820, 748</sup> A positive agglutination reaction in dilution of 1:40 or higher was considered the most reliable sign of infection by Evans, Robinson and Baumgartner. A reaction at this titer does not often occur in cases with no history of brucellosis. [At The Mayo Clinic titers below 1:160 are usually not considered significant; in all cases titers must be interpreted in connection with clinical data.—Ed.] Agglutination reactions at a titer of 1:40 were obtained for 3.2 per cent, of 1:80 for 1.6 per cent of 316 persons ill with other diseases, for none of 26 healthy subjects.<sup>290</sup> Of 5000 blood serums routinely submitted for Wassermann tests in a general hospital (Denver) 51 showed brucellosis agglutinins at titers of 1:25, 9 of 1:100, a total of only 60 or 1.2 per cent.<sup>352</sup> Of 170 apparently healthy children none had positive reactions (titers 1:20 to 1:100).<sup>571</sup> But a negative reaction (i.e., a titer below 1:40) does not prove the absence of the disease; almost half of the chronic cases react negatively.<sup>290</sup> Furthermore, in acute cases the test may not become positive until after three weeks of disease.<sup>235</sup> Infected guinea-pigs show agglutinins the ninth day.<sup>140</sup> An improved technique, using stained antigens, was reported.<sup>668</sup>

*Skin Tests.* These were considered the most reliable by some<sup>320, 426, 524, 646</sup> but less reliable than agglutination tests by others.<sup>290</sup> In one series positive skin reactions were found in 93 per cent of patients who had had brucellosis, in 61 per cent of those with chronic brucellosis, in 14 per cent of persons sick otherwise and in 11 per cent of healthy persons.<sup>290</sup> False positive reactions occur not infrequently (in 18 per cent) among tuberculous children.<sup>571</sup> Among 491 patients in a general hospital 12 per cent

had positive reactions.<sup>352</sup> Tests with heat-killed vaccine produce more severe reactions than those with brucellergin. Using the latter, positive reactions were found in 9 per cent of 7122 Kansas City school children; the percentage incidence of positive tests increased with age.<sup>81</sup>

*Opsonophagocytic Test.* Evans<sup>288</sup> found this test practical but one to be interpreted carefully. But she and her colleagues<sup>290</sup> found it the least reliable of the specific tests because of frequent false-positive results (weakly positive in 22 per cent, strongly positive in 9 per cent) among persons ill of other diseases. Because they found strong positive reactions in cases of chronic brucellosis and weak or moderate reactions after recovery they could not confirm the opinion of others that strong reactions indicate immunity and weak reactions indicate infection. In this opinion Keller, Pharris and Gaub concurred. Cain described an improved stain technic for the test.

Clinical and animal experiments by Welch, Wentworth and Mickle indicated that sulfanilamide markedly increases opsonophagocytic activity for *Brucella* organisms. In animals the average percentage of cells showing marked phagocytosis before treatment with sulfanilamide was 20, after treatment 97. Curiously also, in three of five human cases of brucellosis agglutination tests gave negative results before administration of sulfanilamide and positive results afterward.

*Cultures.* "There is no reliable test to detect chronic brucellosis. *Brucella* infections occur in which all three specific tests give negative results. The only proof of brucellosis is the cultivation of the organism—a difficult and time consuming procedure" (Evans, Robinson and Baumgartner). In this connection the case of chronic brucellosis of 25 months' duration studied until death by Menefee and Poston is of great interest. Repeated skin, agglutination, and opsonophagocytic tests gave negative results. Cultures of blood, urine, stool and sputum were also negative for *Brucella* organisms but *Brucella suis* was isolated before death from enlarged lymph nodes and the gall-bladder, and after death from liver, spleen, testes and numerous lymph nodes. Poston described methods used in obtaining cultures.

[This case suggests that if one has good clinical grounds for a diagnosis of brucellosis unsupported by the usual laboratory tests, biopsy and culture of lymph nodes (if enlarged) are indicated.—Ed.]

### TREATMENT OF BRUCELOSIS

*Serums and "Specific" Vaccines.* Five patients, ill from 1 to 13 months, were given polyvalent antimelitensis serum from cattle immunized to *Bacillus abortus* and *melitensis*; all five made a complete recovery within three weeks and remained well (Flippin).<sup>321</sup> Results with Foshay's serum and vaccine seemed "excellent" to Newman<sup>705</sup> in January, "encouraging but not perfect" 11 months later.<sup>707</sup> [No details were given.—Ed.] McIntire considered Brucellin, a filtrate of a broth culture of *Brucella* organisms, superior to Foshay's and other vaccines. Others were not impressed with the value of serums and vaccines.<sup>6, 436, 748</sup>

*Typhoid Vaccine.* Fever reactions with typhoid vaccine seemed useful in two cases of Herndon and three of Etter.

*Fever Therapy.* This therapy gave Newman<sup>705</sup> "encouraging results" (no details). In two acute cases so treated recovery was prompt, but relapse occurred in one.<sup>707</sup> Of nine patients of Prickman, Bennett and Krusen, seven were cured after 5 to 22 hours of artificial fever. Similar cures were noted in 8 of 9 unpublished cases treated by others, and in 2 of 3 published



cases: a total of 17 cures (81 per cent) in 21 cases. Fever therapy must activate man's protective mechanism against the germs since sustained temperatures of 107° F. do not kill *Brucella abortus* in vitro.

*Chemotherapy.* The Abbotts gave from 2 to 13 intravenous injections of metaphen (each 10 c.c. of a 1:1000 dilution) in 10 cases; "in most of them there was a relatively prompt decline in temperature and improvement in symptoms." Fouadin (trivalent antimony compound) "cured" one patient (Thomson)<sup>953</sup> but not two others (Manson-Bahr; Punch).

Sulfanilamide appears to be the most promising remedy. Striking recoveries followed its use in eight cases treated in Europe during 1936 to 1937 (listed by Blumgart). Analysis of some of these reports suggests that the patient may have been entering a period of remission or recovery when treatment was begun (Sheppe). But even so, further experience seems to indicate that the drug is truly effective. Twenty reports during 1938 gave results from sulfanilamide in 60 cases of acute and chronic brucellosis: 52 (87 per cent) were "cured," generally promptly within four to seven days. The largest series of cases (20) was that of Newmann. He first gave prontosil intramuscularly (5 c.c. on alternate days) to four patients. None was benefited, probably because the doses were small. Then to 16 patients he gave sulfanilamide orally (to children four "tablets," to adults six "tablets") daily for eight or more days: 15 were cured in from 2 to 20 (average 7) days; only one failed to respond. The only other failures were in 2 cases of Herndon in which small doses were given, and in one case of O'Reilly in which only 90 grains in four days were used. Cures were reported in five cases each by some,<sup>343, 953, 1019</sup> in three each by others,<sup>617, 910</sup> in two each by others,<sup>330, 331, 803, 961</sup> and in one case each by several.<sup>99, 398, 406, 585, 586, 781, 858, 958</sup>

In most cases sulfanilamide was used alone in oral doses ranging from 60 or 75 grains daily for about nine days to 35 grains daily for about ten days. Several physicians prescribed 60 grains daily for seven to ten days. The use of fairly large doses was advocated by Stern and Blake and by Welch, Wentworth and Mickle (e.g., daily dose: 90 grains for five days, 120 grains for five, 60 grains for three). But rapid results were sometimes noted from smaller doses: fever disappeared within 36 hours in a case after administration of 105 grains (Stern and Blake); a patient of Traut and Logan, critically ill, jaundiced and in stupor, was given a transfusion, and 30 grains of sulfanilamide daily, and became afebrile in 48 hours. The combination of sulfanilamide (oral) and prontosil soluble (subcutaneous) was used by some.<sup>331, 406, 781, 803</sup> Usually only one course of medication was required; occasionally relapses occurred but prompt response followed a second course.<sup>343, 803</sup> Hence some<sup>803, 953</sup> recommended the routine use of one to three follow-up courses, each a week long, within two or three months of the "cure."

Studies by Francis suggested that *Brucella abortus* in vitro is much more susceptible to sulfanilamide than *Streptococcus pyogenes*. That the drug seems to increase opsonophagocytic activity markedly has been mentioned.<sup>1019</sup>

"Prosepticine" (benzyl sulfanilamide: 0.75 to 1.5 gm. daily for seven days) was used by Bevan to cure one case in a child 5½ years old.

*Prophylaxis.* Any solution of the problem of undulant fever which protects man but ignores the vast economic problem of Bang's disease in cattle is but a makeshift remedy. Universal pasteurization is an artificial barrier, not always practicable and won't be attained in our lifetime (Anderson).<sup>28</sup> Measures to prevent the spread of the disease among cattle and to protect dairymen, butchers and veterinarians were discussed.<sup>28, 349, 706</sup> The disease can be spread, not only by unpasteurized milk, but by butter, cheese and ice cream made from such milk.<sup>748</sup>

#### TYPHOID ARTHRITIS: "TYPHOID SPINE"

Typhoidal involvement of the spine is said to occur only once in 1800 cases of typhoid fever. It is now quite rare. Swart reported a case in which osteitis developed rather than an osteomyelitis: destruction of the intervertebral disk between the second and third lumbar vertebrae, and the adjacent borders of the vertebral bodies. Spinal symptoms began two months after the onset of typhoid fever, one month after convalescence therefrom. Recovery was expedited by traction in hyperextension on a convex frame; later a hyperextension cast, then a Taylor brace were used. Supports were discarded at the end of eight months; the patient "was apparently completely well in one year."

#### MENINGOCOCCIC ARTHRITIS

An interesting synopsis of the literature on this condition from the time of Welch (1810) was presented by Schein who reported 23 new cases. The incidence of articular lesions in meningococcic infections has varied from 4.8 to 20 per cent in different epidemics; it was recently 7.7 per cent at Bellevue Hospital. Articular lesions were classified thus: (1) an early, often premeningitic, polyarthritic or arthralgic form; (2) the usual post-meningitic monarticular form; (3) a type resembling serum sickness and (4) occasional postmeningitic spondylitis. Intermediary and atypical forms abound.

*Type 1.* In these cases the mortality is high but there is scant articular involvement. When it does occur, it may be in the form of polyarthritis or polyarthralgia resembling rheumatic fever or gonorrheal "rheumatism." It occurs either during the first few days of the general infection or may antedate it. If the latter occurs, diagnosis is especially difficult. Joint symptoms are often transient and are due to peri-articular and intra-articular petechial hemorrhages. Symptoms may include severe pain, marked redness, tenderness and spasm; swelling is slight or absent. It is associated often with a severe hemorrhagic skin rash and a fulminating severe infection. The general prognosis is poor; that of joints is good.

*Type 2.* The usual type is that of true meningococcic arthritis with gross articular damage. One joint is usually affected alone or dominantly. Symptoms appear occasionally with, or one or two days before, the onset of the general infection, but they usually appear after the fifth day of the general infection. There is usually a

marked purulent articular effusion in which meningococci are often found, but there is relatively little pain, redness, tenderness or spasm. Synovial fluid contains excess polymorphonuclears and protein. In this type the general disease is less severe and the mortality lower than in type 1; the general prognosis is good but that for the affected joint is poor. Contrary to previous observers Schein frequently noted irreparable articular damage in adults, but not in children under 12 years of age.

*Type 3.* Included are cases of mild articular involvement due to or resembling serum sickness. Symptoms appear after the sixth day of the general disease, and one or several joints are affected with serous arthritis; cultures of joints are negative. Pain, redness, swelling, tenderness and spasm are all moderate. There may be an urticarial or erythematous skin reaction. If this type of meningococcic arthritis occurs in the second week of disease about the time when serum sickness frequently occurs, differentiation is difficult but not particularly important because either type of articular reaction (type 3 or serum sickness) is fairly mild and the prognosis excellent. Schein concluded that most cases of this type are from the disease, not the serum.

*Type 4 (?)*. A few cases of "post-meningitic spondylitis" have been reported: localized osteo-arthritic lesions affecting two adjacent vertebral bodies and their intervening disk. They may represent a true meningococcal entity, but Schein suspected that some such cases result from damage to disks from repeated spinal punctures.

In the usual (type 2) form the site of involvement in Schein's cases was knee in nine, hand in seven, elbow in six, wrist in five, ankle in four, hip in three, and tarsus in one case. Marked destruction affected two elbows, two hips, a wrist and a knee. Death, unrelated to joints, occurred in three of the 23 cases.

Among 191 cases of meningococcic meningitis seen by Bolduan were 16 of "arthritis" (no details). In Corbett's case of meningitis (of unidentified bacterial type) hands, ankles and wrist were swollen and painful. Many joints were affected mildly in Lambie's case of meningococcal bacteremia.

*Treatment.* Schein treated the general infection by serum, and recommended the use of Hoyne's antitoxic antiserum as a remedy which lowered the incidence of complications, including arthritis. Articular lesions were treated by aspiration, splinting, occasionally traction.

*Sulfanilamide.* Further reports testify to the "profound effect" which sulfanilamide has on meningococcic infections. Among 205 cases of meningococcic meningitis (none with arthritis) cited and treated by sulfanilamide alone<sup>48, 66, 85, 116, 228, 515, 677, 913, 1037</sup> or in combination with serum,<sup>80, 85, 112, 116, 486, 497, 677, 681, 712, 884</sup> there were only 17 deaths. Whether the drug was used alone or not, recoveries were generally prompt and complete, rapid sterilization being accomplished. The following figures indicate that sulfanilamide is as effective, indeed perhaps more effective than serum: Of 75 patients treated by Stevens with serum 43 per cent died; of 17 patients given the drug, only 18 per cent died. Banks noted the death of 16 per cent of 38 patients given serum alone, of 12 per cent of 59 given serum and sulfanilamide, of 6 per cent of 60 given the drug alone. Smith, Maxson and Murphey noted a reduction of mortality from 41 to 13 per cent when the two remedies were used rather than antitoxin alone. Some physicians con-

cluded the combined therapy (drug and serum or antitoxin) was superior to the use of either alone; others concluded that sulfanilamide could be used alone with confidence in all but the most serious cases. Some gave the drug orally, subcutaneously and intrathecally in varying doses according to the severity of the disease. Others insisted it was not necessary to give it intrathecally, perhaps not even subcutaneously, the oral use being sufficient.<sup>681, 1037</sup> One of Willien's patients who failed to recover with \$500.00 worth of serum given in 41 days was cured in 14 days by the use of \$2.00 worth of sulfanilamide.

Further studies on the inhibiting effect of the drug on meningococci in vitro<sup>699, 700</sup> and on experimental infections<sup>298</sup> were reported.

Persons in attendance on patients having meningococcic infections seemed to be protected by taking 45 grains of the drug daily for six days (Bickel). Some recommended that it should also be given to carriers.<sup>681</sup>

Other sulfonamides. Of 11 patients with meningococcic meningitis who received proseptasine, soluseptasine or both, nine recovered.<sup>414, 1040</sup> Six cases of meningococcic meningitis (Hobson and McQuaide) and one of meningococcal septicemia presenting a picture of "acute rheumatism" (Dimson) were successfully treated with sulfapyridine.

[Many physicians now consider sulfapyridine superior to sulfanilamide in meningococcal infections.—Ed.]

3 Fever therapy. A case of meningococcal septicemia hypersensitive to serum was cured by fever therapy (Rosenbluth and Stetten).

#### SUPPURATIVE (PURULENT, SEPTIC) ARTHRITIS

A case of septic arthritis affecting the knee of a child with femoral osteomyelitis was reported (Cutler). *Staphylococcus aureus* was recovered. Orthodox treatment was briefly reviewed.

#### ARTICULAR DISEASE DUE TO HEMOLYTIC STREPTOCOCCI

Formerly a fairly large proportion of cases of septic arthritis was due to hemolytic streptococci, but since the advent of sulfanilamide this type of septic arthritis already seems to be disappearing. Only one instance of this complication was noted among many current reports of conditions due to these bacteria. In a case of hemolytic streptococcal infection reported by Butler<sup>147</sup> acute arthritis of a knee developed; perfect function was obtained after the use of prontosil and aspiration. This illustrates again the supreme importance of making bacteriologic diagnoses as often and as early as possible in all cases of septic arthritis and of course in all cases of septicemia or localized sepsis.<sup>652, 739</sup> Bliss, Long and Feinstone described clearly the criteria for the recognition of the main streptococcal groups. Physicians who are confused by current bacterial terminology will find their paper especially useful.

*Sulfanilamide.* Further studies on the mode of action of the drug on beta hemolytic streptococci were reported.<sup>479, 541-591, 606</sup> The drug proved

very potent in saving animals with experimental hemolytic streptococcal meningitis.<sup>12, 544</sup> Even when local lesions were not fully controlled, the drug seemed to prevent bacterial invasion of the blood stream. [Hence the diminution of articular complications.—Ed.] Striking results were noted in the treatment of patients with various hemolytic streptococcal infections, including many cases of meningitis, the mortality rate of which has been reduced from about 92 to 97 per cent to about 14 per cent (McGinty). These references concern the excellent results in erysipelas, mastoiditis, otitis, and hemolytic streptococcal pneumonia but especially meningitis, all of which diseases formerly were frequently the cause of complicating arthritis.<sup>30, 33, 116, 147, 150, 174, 192, 293, 366, 391, 400, 461, 515, 575, 627, 677, 845, 913, 942</sup>

A case of *anaerobic* beta hemolytic streptococcal meningitis was also successfully treated with sulfanilamide.<sup>882</sup>

Neoprontosil (prontosil soluble) was used orally to treat successfully cases of hemolytic streptococcal sore throat, nasopharyngeal carriers, and two cases of septicemia intolerant to sulfanilamide (Herrell and Brown).

#### ARTHRITIS OF SCARLET FEVER: POSTSCARLATINAL RHEUMATISM

Opinions are still in conflict as to the value of sulfanilamide in scarlet fever. Hogarth concluded that it had no effect on fever, toxemia or incidence of complications. Acute scarlatinal rheumatism affected two of 115 patients given no special therapy, none of 126 patients given serum, and one of 114 patients given serum and sulfanilamide (generally small doses of the latter). In the three groups the total complications numbered 31, 29 and 25 respectively. Sako, Dwan and Platou, using larger doses of sulfanilamide, noted definitely beneficial results. Complications affected 41 (two with "arthritis") among 100 patients with scarlet fever not given sulfanilamide, but only eight (no arthritis) among a similar number given the drug. However, the duration of toxemia was not shortened thereby, hence combined serum and drug therapy was recommended. The latter also had a prophylactic value which antitoxin alone did not. Maxcy's report on changing concepts of scarlet fever is of interest.

#### ARTHRITIS WITH CHRONIC ULCERATIVE COLITIS

Subacute or chronic arthritis complicates about 4 per cent of cases of this disease. For reasons previously<sup>3</sup> given some physicians have concluded it represents a special entity, not merely a variety of ordinary atrophic arthritis. A woman in her fifth year of chronic ulcerative colitis first had "recurrent bouts of pain and swelling in practically all the joints of her extremities." Temporarily improved by conservative measures the disease progressed slowly until nine years later pelvic abscess and partial intestinal obstruction developed. After colectomy the intestinal and articular symptoms subsided (Campbell).

[Two years later abdominal symptoms were still absent but she experienced an acute attack of arthritis which subsided shortly after the use of irrigations to the remaining segment of the colon.—Ed.]

Preliminary experiences suggested that neoprontosil (prontosil soluble) given orally has a beneficial effect on this disease.<sup>49, 125, 437</sup> Others<sup>624</sup> found the oral use of prontosil soluble less effective at least in dogs, than its subcutaneous use. It was absorbed poorly from the intestines, and concentrations in blood were relatively low.

#### RARER FORMS OF SPECIFIC INFECTIOUS ARTHRITIS

1. The articular complications of the different dysenteries (bacillary, amebic) were considered by Benjafeld and Halley, who reported the case of a girl with nonsuppurative destructive arthritis of a hip. Various bacteria isolated from the throat were considered insignificant, but pure cultures of an organism of the "*Flexner dysenteric type akin to Bacillus alkalescens*" were repeatedly recovered from feces despite the absence of dysenteric symptoms. The patient whose arthritis had been treated unsuccessfully for 10 months by immobilization, "recovered rapidly" when intestinal antiseptics, colon irrigation and vaccine were used.

2. Bishop reported the case of a child with burns on a foot infected with *Bacillus pyocyaneus*. The ankle was drained and apparently healed, but 15 months later the acute pyarthrosis recurred. From the incised ankle pure cultures of the bacillus were recovered. Only one similar articular infection (Pinelli, 1927) has been reported.

3. *Micrococcus catarrhalis* (*Neisseria catarrhalis*) is rarely a serious pathogen. Solomon and Tuchewicz saw a woman, aged 64 years, with acute arthritis of a knee with much swelling and pain in the joint and leg, also a foul vaginal discharge, polyuria and dysuria. Gram-negative intracellular diplococci were found in the cervix and naturally thought to be gonococci. The morphologic characteristics of *Micrococcus catarrhalis* and gonococci are identical. Similar organisms were grown from the aspirated purulent synovial effusion but were proved by various tests and fermentations to be *Micrococcus catarrhalis*, not gonococci. Treatment (aspiration, immobilization, heat, later massage and exercises) resulted in "complete restoration" of articular function. Curtis (1932) reported a case of bacteremia and acute polyarthritis from this organism.

4. The day after falling out of bed an infant had fever and acute arthritis of a hip, wrist and elbow. Therein purulent effusions developed from which *Hacmophilus influenzae* and *Corynebacterium xerosis* were recovered by Weaver and Sherwood. Roentgenograms of wrist and elbow remained negative; dislocation of the femoral head occurred and was corrected by incision and open reduction. Within a month complete motion of affected joints was restored. Acute purulent monarthrititis of a knee in an elderly woman was noted. *Hacmophilus influenzae* were recovered.

This organism can produce pus, and has been the known cause of many suppurative processes, notably meningitis. Previously reported have been 11 cases of hematogenous pyarthrosis with influenzal meningitis and 13 cases without meningitis, practically all being in infants. From one to three joints were affected in each case. Weaver and Sherwood noted that all cases with meningitis were fatal; in all others, except one, recovery occurred, generally with excellent articular function regardless of the treatment used (aspiration, incision, lavage and closure of joints; aspiration and injection of tripaflavin or Carrel-Dakin solution).

### RHEUMATIC FEVER

Several useful reviews of the subject appeared, notably a comprehensive one by Swift and McEwen on all phases of the disease and an analysis by Schlesinger of 1000 cases of rheumatic carditis. The disease appears to be notably on the decrease in London.<sup>234</sup>

*Predisposing Factors.* 1. Geography and climate. According to Mills "rheumatic infections, and their resulting disabilities are perhaps more directly and completely conditioned by climate and weather characteristics than are any other disease states." Differences in death rate from the disease in the northern and southern states of the United States are much less striking than the differences in its incidence. Two American regions of greatest mortality are the Rocky Mountains and higher plateau states to the east, and from Iowa eastward to the coast. The survival rate of the "more vigorous people of the north" seems to be notably higher. Grinnan noted the incidence of the disease among admissions to a general hospital in Norfolk, Virginia, to be 0.25 per cent (compared to 0.9 per cent in New York City). Cardiac damage seemed to be less severe; otherwise the disease in Virginia was similar to that elsewhere. Altitude seemed a more important factor than dampness in France where the disease is more frequent in the higher center and east than in the damp west plains, but marked variations were seen in the same regions.<sup>210</sup> Further reports indicate the widespread nature of the disease.

It is not uncommon in the tropics and is commonly seen in South Africa<sup>207, 314</sup> and India.<sup>455, 614, 920-922</sup> Among 10,937 cases which came to postmortem examination in the medical college hospitals of India, Stott found the incidence of mitral endocarditis (largely rheumatic) to be 2.2 per cent, and to be 14 per cent of the cases of circulatory diseases.<sup>922</sup> In King George's Hospital, Lucknow, India, the "incidence of acute rheumatic infection" was 6 per 1000 medical admissions: 42 per cent were for acute rheumatic fever, 52 per cent for acute carditis, 6 per cent for chorea.<sup>921</sup> In another Indian hospital the rate was 1.2 per 1000 medical admissions.<sup>614</sup> The disease in India resembles that elsewhere except that its age incidence seems to be extended somewhat as compared to Europe, and rashes, chorea, and nodules were rare (Hodge).

In England Poynton regarded the factor of "macro-climate" (rain, mist, fog, cloudiness, cold, damp) not as important as that of the "micro-climate" of the patient's home (cold, damp homes, overcrowding, poor sanitation and nutrition). Hill<sup>443</sup> stated that climate per se has little influence on the incidence of the disease. Eskimos

and Laplanders are remarkably free of it. The factors of crowded, warm rooms, and infection spread by "carriers" are more important than variations in natural climate. According to Edstrom, the incidence of rheumatic fever in Europe is influenced not so much by dry or wet climate per se as by the passage of cyclones and anticyclones affecting the vegetative nervous system. Of interest in this connection is Poulton's consideration of the effect of wet and dry climates and weather in the causation of disease.

2. Season. Although the incidence of rheumatic fever in England is influenced by damp cold, the disease is most frequent in hot, dry years: Rowlands reconciled this apparent discrepancy by noting that the disease is most frequent after or during marked changes in humidity and temperature. The high fall incidence is related to the rapid decrease in temperature and increase in humidity. Mills concluded that the seasonal incidence in such widely scattered regions as San Francisco, Peiping (China), and Cincinnati was related to the storm waves in those areas. Stott noted the seasonal incidence in India.

3. Social and hygienic factors. Although the factor of overcrowding was notable, the family income was "adequate" in 164 of Dally's 300 London cases of juvenile rheumatism. Poynton also frequently saw the disease among children who were not poor; nevertheless, the incidence was less than that among the poor. Acute rheumatism was very uncommon among 75,000 adults and juvenile inmates of 60 British mental institutions who were well housed, well fed, well clothed, led regular lives, were segregated and under constant medical supervision. Tonsillitis, however, was frequent. Their ideal "micro-climate" was probably responsible for their exemption from rheumatic fever (Poynton).

4. Family, heredity, constitution. In England a hereditary factor is present in about 40 per cent of cases (Poynton). Read, Ciocco, and Tausig noted the incidence of rheumatic symptoms (chorea, rheumatic fever, rheumatic carditis) among the relatives of 33 rheumatic and 33 nonrheumatic children. Rheumatic symptoms affected 16 per cent of the siblings, 31 per cent of the parents, 9 per cent of the uncles and aunts, and 18 per cent of the grandparents of the rheumatic children, but only 4 per cent of the siblings, 8 per cent of the parents, 4 per cent of the uncles and aunts, and 2.3 per cent of the grandparents of the nonrheumatic children. That such a familial tendency was manifest for at least three generations strongly suggested a constitutional susceptibility to the disease. This does not eliminate the possibility that exposure is also an important factor. According to Gibson,<sup>356</sup> rheumatic fever does not behave as a familial disease, although it is more prevalent in some families than others; some factors in the individual child determine his tendency to the disease. Of interest in this connection is the report of Morgan and Webster of the occurrence, within two weeks, of rheumatic fever and mitral endocarditis in each of identical twins, and that of Holsti and Huuskonen on the frequent appearance of atrophic and hypertrophic arthritis and rheumatic fever among four generations of one family.



A common belief in England, recently contested (Brownlee, 1927) is that the disease develops more often among blonde and blue-eyed children than among brunette, dark-eyed children. Among Dally's 300 cases, the eyes were gray in 121, brown in 91, hazel in 53, blue in 35; hair was medium-colored in 115, dark in 96, fair in 80, and red in 9. Lack of controls makes such data of little significance, according to Findlay. Rheumatic children have a characteristic constitution, according to Dally, featured by "a decreased alkaline reserve in blood, and in urine, a deviation of the acid base balance in the direction of increased acidity."

[No proof for this idea was given.—Ed.]

In contrast to this view was that of Findlay<sup>308</sup> who stated that the "pre-rheumatic child" cannot be definitely diagnosed; indeed, his existence seems unlikely: "the term should be allowed to lapse. . . . There is nothing in the make-up of the body, either physical or chemical, which enables us to foretell the possible development of [rheumatic fever]. One must never forget the common environmental conditions of the various members of an individual family as a possible factor in this event." Contrary to the belief of others, according to Findlay, chorea does not particularly affect clever, high-strung children, and nervousness, enuresis, and digestive disturbances are not frequent precursors of rheumatic fever.

5. Sex. Of Dally's patients, 117 were boys, 183 girls. Most cases in India are in men, but this is of no significance, as Indian women receive much less medical care than men (Stott).

6. Age. In current reports the usual age incidences were reported. Eigen reported the fatal case of an infant 32 months old: a study of the rheumatic pneumonitis and myocarditis present suggested that the disease began when the infant was between 18 and 24 months old. "It is probable that first attacks of rheumatic fever frequently occur at a much earlier age than has been suspected."

*General Symptomatology.* The symptomatology of the disease in children (juvenile rheumatism) and in adults was again described.<sup>34, 308-310, 356, 581, 1001, 1042</sup> According to Findlay in juvenile rheumatism only four [common] manifestations are unquestionably due to the rheumatic toxin: arthritis, chorea, carditis, and subcutaneous nodules. None of them alone is pathognomonic of the disease, but when two or more of them are seen in combination or in sequence, then "the clinical picture is one of the most characteristic in the whole domain of pathology." Contrary to the view of many Findlay strongly opposed the view that rheumatic fever ever produces meningeal, pleural, pulmonary, or peritoneal infections. He considered erythema circinatum a rare but true rheumatic manifestation, but not erythema nodosum.

The relative frequency of the various symptoms of the disease as reported in new series<sup>34, 234, 581, 1001</sup> was about as stated in previous Reviews: polyarthritis and carditis respectively affected 135 and 122 of Archer's 150 patients, whose average age was 18 years. [In several large American series of cases the average age of onset of the disease was between six and ten years.—Ed.] Articular symptoms were much more frequent among Dally's juvenile pa-

tients than among those of Litchfield. Chorea affected 9 per cent of Archer's patients; it was an early symptom in 1 per cent of Dally's cases. In juvenile rheumatism the clinical picture is often not that of an acute febrile polyarthritis with carditis, but that of a low-grade chronic infectious process producing fatigue, muscle and joint pains, swollen lymph nodes, frequent colds, nose bleeds, and so forth, often with few or no laboratory abnormalities (Wolffe and Digilio).

Contrary to older views, most "growing pains" of children are now considered not rheumatic, but due to various juvenile orthopedic lesions or to the fatigue from hard playing.

Dally distinguished three types of juvenile "growing pains": (1) the largest group in which nonrheumatic pains often were associated with fatigue, irritability, and anemia, or due to postural or minor orthopedic defects (flat foot, knock knee, scoliosis) and to debility after severe illness or to psychologic maladjustment; (2) muscular or tendinous pains due to chronic rheumatism, not to chronic rheumatic fever (sedimentation rates normal or essentially so); (3) pains, which are generally articular, due to true subacute or acute rheumatic fever; several joints in succession may become painful and swollen, and there is usually some fever and an altered sedimentation rate. Nonrheumatic pains are more likely to be muscular, are generally short-lived, but frequently recur over a fairly long period of time. Rheumatic pains are more likely to be articular, less recurrent, more persistent, and often severe enough to confine the patient to bed for a couple of days. If carditis is to appear, it does so fairly soon; one is not left in doubt long (Findlay).

Excess fever (rectal 109° F.) was the unusual complication which affected a 40 year old patient of Boone: at necropsy rheumatic valvulitis, cerebral engorgement, thrombi, edema and a small pituitary hemorrhage were found.

#### GENERAL CONSIDERATIONS ON THE PATHOLOGY OF RHEUMATIC FEVER

The general pathologic changes of the disease were described by Collins<sup>202</sup> as occurring in three phases. The pathologic reactions of phase 1 occur at the height of activity of the rheumatic process, are nonspecific (diffuse or petechial hemorrhages into serous membranes, skin, bowel, or lungs; increased capillary fragility; regions of focal necrosis in parenchymatous organs) and are merely evidences of an intense toxemia. In phase 2 specific rheumatic reactions occur: granulomatous lesions which form in connective tissue and later undergo fibrosis develop within a week or so of the rheumatic attack, and are much more frequent than the acute nonspecific reactions. In this phase, four different processes regularly participate in varying degree: exudation, proliferation of mesenchymal tissues, degeneration of connective tissue, and infiltration of leukocytes. Details of these processes were described. Reactions in phase 3 are nonspecific and include changes in organs resulting from chronic carditis.

## SPECIAL CLINICOPATHOLOGIC DATA IN RHEUMATIC FEVER

1. *Cardiovascular System.* Of Findlay's 559 cases of acquired carditis, at least 96 per cent were rheumatic in origin. During 1936 in Philadelphia 357 deaths were reported as certainly due to, and 195 other deaths, as probably due to, rheumatic carditis. The mortality rate from rheumatic carditis was 17.6 per 100,000 population, excluding the 195 probable cases, or about 25 to 30 per 100,000 population including them (Hedley).<sup>429</sup> Among persons under 20 years of age, rheumatic carditis caused more deaths than pulmonary tuberculosis, and more deaths than whooping cough, measles, meningococcal meningitis, diphtheria, scarlet fever and anterior poliomyelitis combined. In Hedley's series, the mean age at death in all cases of rheumatic fever was 36.5 years.

To improve the national statistics on this disease, the United States Bureau of Census has made certain changes in the method of tabulating cardiac deaths.<sup>258</sup>

The incidence of rheumatic carditis among 104,163 students at 86 American colleges and universities was reported to be 11.6 per 1000 (9.5 per 1000 men, 14.9 per 1000 women). Hedley<sup>428</sup> reported the statistics from individual coöperating institutions. The reported incidence was largest in the smaller schools, smallest in the larger schools with well organized health services and frequent examinations of students. In the latter colleges many tentative diagnoses of carditis were discarded after the use of specialized studies not available in the smaller colleges. In other words, the reporting of a true incidence depends not so much on case-finding as on the detection and proper interpretation of murmurs and other physical signs.

According to Findlay,<sup>310</sup> if a murmur is located, or has its seat of maximal intensity, at the base, it is probably functional, but if the murmur has its seat of maximal intensity at the apex and particularly if it is propagated to the left, it is probably organic. Schlesinger<sup>833</sup> discussed the significance of systolic and diastolic murmurs in juvenile rheumatism at some length and stated that both mitral and aortic diastolic murmurs eventually disappear in some patients. McKee agreed with this conclusion as a result of his stethographic studies on 130 rheumatic children and 105 normal controls. Stethograms (Lockhart method) provide graphic evidence of the exact timing, intensity and vibration rate of murmurs.

Statistical studies were presented concerning the relative incidence and types of rheumatic valvulitis in England<sup>787, 833</sup> and in India.<sup>614, 921</sup> An extensive correlation of the electrocardiographic and pathologic findings in 113 fatal cases of rheumatic mitral disease was made by Berliner and Master. Calcareous aortic stenosis occurred much more frequently than is generally supposed; until recently its etiology was obscure. The data of Clawson, Noble and Lufkin, and of Willis and Dry, who studied 200 and 228 cases respectively, indicate that it is unquestionably a rheumatic lesion. Its symptoms and signs were described in detail. Complete heart block rarely occurs in acute rheumatic fever. Wedd described a case: during one period of syncope death seemed imminent. The patient failed to respond to epinephrine, but recovered regular ventricular rhythm after an intramuscular injection of 2 mg. of atropine.

Among 500 children with rheumatic fever or chorea, Taussig and Hecht noted 49 with definite hypertension (diastolic over 90, systolic generally over 130). In 12 cases hypertension was transient and blood pressures fluctuated widely; in 37 cases the elevated blood pressure occurred with the acute rheumatic episodes. None of the patients had nephritis. Among Dally's 300 juvenile patients, arterial pressures were generally normal.

2. *Joints*. Collins published new photomicrographs of the characteristic changes in joints. The paucity of cellular proliferation and the manner in which synovial tissues "always completely recover" differentiate this lesion from that of atrophic arthritis.

3. *Nodules*. Subcutaneous nodules appear on children more frequently than on adults: 14 per cent of Keil's <sup>521</sup> 181, and 10 per cent of Anderson's <sup>29</sup> 111 juvenile patients had them but only 4 per cent of Archer's 150 patients, some of whom were adults. The nodules may appear overnight; they are firm, seldom tender, and last from a few days to several months, then gradually disappear. Although they appear in crops, each nodule may last quite a while. Schlesinger noted their persistence for as long as three to five years. When they have apparently "disappeared," they may still persist microscopically. Earlier descriptions spoke of them as varying from the "size of a millet seed" to "that of a Barcelona nut," but their average size was "that of a split-pea" (Barlow and Warner, 1881). Some are "almost impalpable," being essentially microscopic only, hence they must be felt for as well as looked for. They were described currently as the "size of large peas to small granules" <sup>1001</sup> or "pinhead to large marble." <sup>29</sup>

Concerning their prognostic significance, Cheadle (1889) wrote: "The eruption of large nodules is almost equivalent to a sentence of death." This view is still generally held. Of Anderson's 11 juvenile patients with nodules, 10 had carditis. "When such nodules are present, we know the heart muscle is riddled with similar nodules" (Warner). The number of nodules is a rough measure of the "dose" of rheumatic infection present.

Schlesinger noted that children with 10 or less nodules were much more likely to recover (31 recovered, 7 died) than those with more nodules (5 recovered, 12 died). The prognosis was bad if 20 to 40 nodules were present. Of 90 patients with nodules, 40 per cent died generally within three to five years. Nodules were rare in children under seven years of age or after puberty. Before the age of 14 years a child with nodules has only an even chance of survival (33 deaths, 22 recoveries), but after puberty the prognosis is much better. Schlesinger noted many exceptions to these generalizations and concluded that nodules should be regarded with some anxiety but need never be considered a fatal omen.

[In this opinion we concur.—Ed.]

Originally subcutaneous "rheumatic nodules" were regarded as pathognomonic of rheumatic fever; this idea is no longer held by some physicians. Hawthorne and Keil reviewed the controversy as to whether the nodules in rheumatic fever are distinctive or similar to those seen in atrophic arthritis and other conditions. Hawthorne concluded that no absolute distinction has been established. Findlay <sup>310</sup> considered them similar to those of atrophic

arthritis, and did not regard the granuloma as pathognomonic of rheumatic fever: "Like Schmorl I have convinced myself that in many instances the giant cells or the so-called Aschoff bodies are not fibroblasts in origin, but are composed of detached pieces of degenerated cardiac muscle." According to Collins, the nodules are granulomas, "built-up masses of proliferating mesenchymal cells, newly formed capillaries, and areas of fibrinoid degeneration with infiltration of lymph and plasma cells," and they are not exactly similar to those of atrophic arthritis. Using supravital staining, McEwen studied nodules from 11 cases of rheumatic fever and eight of atrophic arthritis, also two syphilitic juxta-articular nodules. On section the "rheumatic" and "arthritic nodules" were "very similar." On supravital staining, in two of the eight cases the arthritic nodules were identical to the orthodox nodules of rheumatic fever, but in six cases minor variations were noted. Both types were different from syphilitic nodules. Keil concluded that the rheumatic nodules are sufficiently different from those in atrophic arthritis to warrant their distinct separation.

4. *Lungs and Pleura.* In some cases of rheumatic fever, migratory areas of pulmonary consolidation suddenly appear, last a variable length of time, disappear as quickly as they come and, according to some, produce no change in the clinical picture and no variation in pulse or respiration. Physicians agree on the type of pathologic reactions found, but disagree as to whether or not they are specific for the disease. Melnick examined the lungs in six fatal cases at Cook County Hospital, Chicago. Lungs were involved in a "vascular reaction of great intensity, backed up by a cellular proliferation. In the areas of greatest intensity the endothelium of the smaller vessels is injured." The process is not simply passive congestion; it is chiefly a focal process, not one of the simple inflammatory type as there are no bacteria and no necrosis. Melnick considered the reaction a hyperergic one. Continuing his studies on "rheumatic pneumonia," Gouley reviewed its pathologic features (as given in previous Reviews) and suggested that such pulmonary lesions may be an important factor in subsequent right ventricular failure. The latter is supposed to result from mitral stenosis and increased pressure in the pulmonary circulation. Gouley concluded that sometimes the chief factor in right ventricular failure is increased pulmonary pressure from the pulmonary changes themselves, a diffuse fibrosis which originally results, not from passive congestion, but from chronic rheumatic interstitial pneumonitis.

[Before accepting this view, one must recall that pulmonary fibrosis of much severer grades than that seen in rheumatic patients may occur in other diseases without right ventricular failure.—Ed.]

5. *Skin and Mucosa.* Among 523 cases of rheumatic fever and carditis, Keil<sup>520</sup> noted 181 eruptions in 163 cases listed thus: 53 rheumatic erythematous eruptions, 53 various hemorrhagic eruptions, 36 subcutaneous nodules, 11 telangiectatic eruptions, 8 scarlatiniform, 7 urticarial, 5 of erythema nodosum, 5 sweat eruptions, 3 herpes zoster. Some of these were rheu-

matic, others were not. Keil classified the 53 cases of rheumatic erythema ("rheumatic erythema multiforme") as follows: (1) a simple papular form, "erythema papulatum rheumaticum" in 14 cases; (2) ringed forms: (a) erythema marginatum rheumaticum in 15 cases; this is the most characteristic rheumatic erythema and (b) a flat "erythema annulare rheumaticum" in 24 cases. Their differing locations and appearance were described in detail. They were all transient, generally lasted from a few hours to several days; rarely for months or even years. They all indicate the presence of active rheumatic disease.

[This is a very thorough review of the subject.—Ed.]

Erythema marginatum (multiforme or circinate) affected only 13 of Schlesinger's 1000 patients with juvenile rheumatic fever. The outcome in these cases was so good that the advent of a circinate rash, even with nodules, appears to be, if anything, a welcome sign.

[There probably are exceptions to this rule.—Ed.]

Erythema annulare rheumaticum usually appears, according to some, after rheumatic carditis has occurred, during the subsidence of rheumatic infection or between recurrent attacks, and is of little prognostic import, since its severity does not parallel that of the general disease. Abramson and Tunick disputed these views; they reported two cases in which the skin lesion appeared as an initial symptom of rapidly fatal rheumatic fever; the severity of the erythema reflected that of the general disease.

Barber introduced a general discussion by several speakers on the skin manifestations encountered not only in rheumatic fever, but in other rheumatic diseases (atrophic arthritis, gout, etc.).

6. *Abdomen.* Contrary to the opinion of Findlay,<sup>310</sup> Warner considered rheumatic fever capable of inducing characteristic abdominal symptoms, and noted three children with acute rheumatism erroneously operated on for acute appendicitis. The pain is usually present in quick succession in several different regions, e.g., left iliac fossa, the epigastrium, right iliac fossa, or left hypochondrium. Antecedent or concurrent limb pains may be absent or overlooked. Sison and Austria noted the following three cases of leukocytosis and severe abdominal pain, generally epigastric.

In one case epigastric pain and tenderness, without fever, suddenly developed; they disappeared shortly to recur the next day with fever. The pain was then continuous, at times colicky and sometimes extended to the right hypochondrium. Four days later articular pains appeared; the slight epigastric rigidity and tenderness persisted and later carditis appeared. Symptoms were relieved by administration of salicylates. Tympany and left abdominal pain and tenderness developed in another case 12 days after the onset of mild febrile polyarthritis. A month later *Streptococcus viridans* was recovered from the blood and was possibly related to bacterial endocarditis. In the third case sudden epigastric pain requiring morphine developed; there was no fever. Next day the severe pain recurred with fever, epigastric rigidity and tenderness. Mild polyarthritis and evidence of recurring rheumatic carditis were noted. Symptoms disappeared on rest and administration of salicylates.

[We agree with Warner that such cases are encountered, but consider them infrequent.—Ed.]

Speculations were entertained that the pains may have resulted from peritoneal irritation, or reflexly from involvement of pericardium, pleura or abdominal aorta.

A different type of abdominal pain was present in 10 per cent of the cases of "low grade rheumatic disease" seen by Digilio, Pescatore, and Goldberg, namely, a dull gnawing, pulling, or dragging pain anywhere in the abdomen, but especially in the left upper quadrant which occurred only on locomotion: Perhaps it arose from involved spleen or abdominal lymph nodes. No other symptoms were noted except anorexia and pallor, but joint pains and mild fever often antedated the abdominal pains. Six illustrative cases were described: blood counts and sedimentation rates were normal.

[A variety of so-called rheumatic abdominal symptoms have been noted in previous Reviews. Their position will be uncertain until a pathologic explanation for them is forthcoming.—Ed.]

7. *Kidney.* An elderly patient of Good and Kanee had acute febrile polyarthritis and carditis; a week later headache, nausea, vomiting, acute hypertension and nephritis, later still phlebitis and pneumonitis developed; he died of uremic poisoning.

8. *Brain.* A case of acute hemorrhagic encephalitis and rheumatic fever was noted by Dobbs and de Saram: after death no specific rheumatic changes in the brain were found; "only one other similar case" has been seen (Alpers, 1928).

*Electrocardiograms.* Electrocardiograms were made by McGee in 50 cases of active rheumatic fever; in 46 cases abnormalities were found such as changes in the P-wave, in the P-R interval, widening or slurring of the QRS complex, changes in the S-T interval and depressions or inversions of T-wave. [It was not stated how often tracings were made, what percentages of the total number of tracings were normal, and how early in the disease most of the abnormalities in tracings appeared. In at least five cases the electrocardiographic alterations were detected before frank symptoms of rheumatic fever. One must not always expect to find abnormalities when single tracings are made.—Ed.] Alteration in the P-R interval is accepted as one of the most characteristic features of rheumatic carditis. Keith noted such changes in mild juvenile cases with little or no clinical signs of carditis; they often bore little relationship to the severity of the disease. P-R intervals, increased more than 0.02 second (normal for children, average 0.138 second, range 0.12 to 0.17 second), were noted in 80 per cent of 86 cases of carditis, in 81 per cent of 59 cases of chorea and carditis, in 50 per cent of 43 cases of chorea and carditis, and in 58 per cent of 12 cases of arthritis without clinical evidence of carditis. In other words, an increased conduction time is the most constant and characteristic single cardiac feature of the disease. These conduction defects have been thought due to structural changes in the auriculo-ventricular node. But because they occurred even in very mild cases in which aortic lesions and probably edema of the bundle of His were not present, Keith suggested that

they were due, not to local pathologic reactions or to "toxins" but to overstimulation of the vagus which may be an essential feature of rheumatic fever. The origin of this overactivity is obscure, but its site is probably peripheral, in the terminations of the vagus (parasympathetic nerve endings) in the heart, rather than in the medulla. One rheumatic child had a systolic murmur, lengthened conduction time, repeated abdominal pain and vomiting, sometimes diarrhea. Perhaps the abdominal pain and vomiting occasionally seen early in rheumatic fever without pericarditis are due to overstimulation of the vagal nerve supply to the gastrointestinal tract.

*Blood Chemistry.* Blood sugar. Rheumatic carditis is rarely encountered among diabetic patients. Steincrohn wondered whether hyperglycemia of diabetes mellitus provided a protective state for the heart in the event of rheumatic fever. If so, persons susceptible to, or with, rheumatic carditis might be expected to have low or flat blood sugar tolerance curves; i.e., a high sugar tolerance. Such appeared to be the case in a number of Steincrohn's patients (47 adults with active, chronic, and 11 children with acute, rheumatic fever). Sugar tolerance curves of 24 adults and 9 juveniles were low; indeed, the curves of the latter were practically flat (average of 9 curves: blood sugar fasting 69.5, at one-half hour 90, at one hour 86, at 2 hours, 83, at 3 hours 79 mg. per cent).

Blood cholesterol. Poindexter and Bruger frequently noted hypocholesteremia in 18 cases of rheumatic carditis: blood cholesterol was below 150 mg. in 28 per cent, over 250 mg. per cent in 5 per cent. But the total average cholesterol value in these rheumatic cases was not significantly abnormal. These values contrasted with the hypercholesteremia often present in cases of arteriosclerotic or hypertensive heart disease.

The arithmetical mean for the total plasma cholesterol was 195 mg. per cent in 33 control cases, 185 in 18 cases of rheumatic carditis, 248 in 24 cases of arteriosclerotic heart disease, and 246 in 19 cases of hypertensive heart disease with arteriosclerosis. There was no significant difference in the ratios of ester to free cholesterol in the three types of heart disease. The average ratio of cholesterol ester to free cholesterol was 1.7 in the rheumatic, 1.86 in the arteriosclerotic, and 1.77 in the hypertensive cases.

Changes in blood cholesterol in rheumatic fever were also noted by Offenkrantz. During an acute rheumatic infection or exacerbation, the blood cholesterol, especially the ester fraction, was reduced. Each patient seemed to have his own normal standard and could not be compared exactly with others.

Of 100 patients with rheumatic fever, 49 were in a quiescent stage: their mean value of total serum cholesterol (and standard deviation) was  $181.9 \pm 23.5$  mg. per cent; the mean value of free cholesterol was  $50.5 \pm 7.4$  mg.; the percentage of free cholesterol was  $27.3 \pm 2.2$ . The total serum cholesterol was definitely lowered, and the percentage of free cholesterol was increased (depletion being ascribed to the loss of ester fraction) in 11 cases of acute rheumatic fever without cardiac failure, and in 12 cases of fluctuating activity of disease. In nine cases of active infection with cardiac decompensation and in seven of fluctuating activity, there was a moderate



fall in the total cholesterol values, but exacerbations did not produce the usual rise in the percentage of free cholesterol, indicating a reduction in both ester and free cholesterol. Five patients died: on the day of death or 10 minutes after death, there was a severe loss of esters, but only a slight loss of free cholesterol, so that the percentage of free cholesterol rose above 30 in each instance. Among the total group of 100 patients were five with unusually high values for total cholesterol (189 to 268 mg. per cent) despite active disease. The pattern of their mental behavior seemed to set them apart from the others enough to suggest that "possibly a psychiatric-functional status is associated with a particular type of cholesterol level in the blood."

Such studies may be of importance because experimental work has suggested that lipids participate selectively in antigen-antibody reactions; concentrations of blood cholesterol may constitute a definite factor in the patient's defense mechanism, and depletion of blood cholesterol may affect antibody response.

[The blood cholesterol is generally somewhat low in most chronic infections.—Ed.]

#### RELATIONSHIP OF RHEUMATIC FEVER TO OTHER DISEASES

1. *To Subacute Bacterial Endocarditis.* Holmes<sup>404</sup> reviewed literature comparing the clinical and pathologic features of rheumatic and subacute bacterial endocarditis. Without presenting new data, he concluded that the two conditions are closely related, if not different manifestations of the same disease.

[Most pathologists do not subscribe to this view.—Ed.]

2. *To Chorea.* This will be discussed in the section on chorea.

3. *To Atrophic Arthritis.* Data for and against the idea that rheumatic fever and atrophic arthritis may be variations of the same pathologic process were briefly and inconclusively reviewed.<sup>371, 651, 937</sup> These data will be discussed under "atrophic arthritis." Features shared by the two diseases are of a general nature, often shared by other infections, but specific differences are sufficient to distinguish the two diseases clearly (Meakins).

4. *To Erythema Nodosum.* Although erythema nodosum occasionally accompanies rheumatic fever, Keil<sup>520</sup> did not consider it a feature of the disease or of true rheumatic origin. Among 800 cases of juvenile erythema nodosum, Wallgren saw only one case related to rheumatic fever, a rare but true instance of "rheumatic erythema nodosum." Erythema nodosum was related not infrequently to a variety of diseases of the upper respiratory tract but to active tuberculosis more frequently ("tuberculous erythema nodosum"). No clinical or pathologic distinction was found among the various types of erythema nodosum, hence it was concluded that the disease is a non-specific allergic cutaneous reaction to several infections, possibly also to noninfectious agents. In most cases, however, erythema nodosum in children is, according to Wallgren, related to active tuberculosis. In every case assumed to be non-tuberculous tuberculin tests and roentgenologic examination of chest should be performed to rule out tuberculosis. In two cases of

supposed rheumatic erythema nodosum, Wallgren discovered unsuspected active tuberculosis.

[The conclusions of Keil and Wallgren are at variance with those of most investigators who believe that erythema nodosum results from several causes and occurs as often with rheumatic fever as with tuberculosis. The observed incidence depends largely on the nature of the clinical material under study.—Ed.]

*Differential Diagnosis.* Rheumatic fever must be differentiated chiefly from gonorrheal polyarthritis, from septicemia and pyemia, occasionally from acute leukemia, acute poliomyelitis, or acute brucellosis, also from acute polyarticular gout and several types of acute specific infectious arthritis.<sup>1001</sup> These differentiations have been given frequently.

#### COURSE, PROGNOSIS AND END RESULTS OF RHEUMATIC FEVER

Rae generalized pessimistically as follows: of every 100 children who have rheumatic fever only one-third escape carditis, one-third die within 10 years of the initial attack; for the rest the carditis continues into adult life, killing patients in their prime. New statistics<sup>96, 104, 503, 833</sup> do not appreciably soften this pessimism. Except in the very young the first attack is rarely fatal; most deaths follow relapses from which patients partially or temporarily recover, but usually with a decreased cardiac reserve. Commonest causes of recurrences among Schlesinger's cases were acute tonsillitis or pharyngitis. Other causes were diphtheria rarely, occasionally (in two cases) tonsillectomy itself (how soon thereafter the exacerbations occurred was not stated). Increased carditis or pericarditis was the aftermath of these recurrences. Studying 59 ambulatory patients with presumably "inactive" or "quiescent" disease Juster noted that in most cases the disease is not really quiescent, but is mildly or definitely active, indicating its inherently chronic, progressive nature. Used as evidences of activity were altered sedimentation rates ("the most delicate test"),<sup>833</sup> weight loss, increased pulse rate, fever (not as useful or as frequent a sign as others), increased physical signs, leukocytosis ("the most valuable" sign),<sup>509</sup> appearance of nodes or chorea, and electrocardiographic changes.

Pregnancy has often in the past been regarded as a serious provocative of cardiac decompensation in rheumatic patients, one usually to be avoided. Although she did not minimize its potential seriousness, Hansen expressed the optimistic view that pregnancy has not been proved to affect the average age of death among rheumatic patients; 95 per cent of rheumatic patients will survive pregnancy; radical obstetrical procedures are seldom necessary, and modern methods of controlling or preventing cardiac failure can be applied as successfully to these patients as to those not pregnant. Many factors must be considered before allowing rheumatic patients to undergo pregnancy, and each case must be decided individually (Niehaus).

The prognosis in cases of juvenile carditis under proper treatment is better than is commonly thought, according to Schlesinger.

Of his 1000 patients observed for 4 to 10 years, 82 per cent (817 cases) were alive and well, 6 per cent (60 cases) were ill, and 12 per cent (123 cases) had died. Of the 817 patients who were "alive and well" 245 had "normal hearts." Of those with definite rheumatic carditis, 16 per cent were dead. Of 166 patients with mitral stenosis alone over one-third were ill or dead; of those (46 cases) with mitral and aortic disease, about half were ill or dead. Heart size influenced the prognosis more than the type of valvulitis present.

With the passage of time the situation becomes worse, as shown by Jones.<sup>508</sup> Among 1000 juvenile patients observed by Jones for an average of 10 years, by the time of their first discharge from the hospital 672 had evidence of carditis, 328 had not and hence were classified as "potential rheumatic heart disease subjects." Of the latter group 77 per cent were subsequently still free of evident carditis. Of the 672 patients with carditis, 34 per cent had died by the time of Jones' report, the condition of 28 per cent was "unchanged," of 18 per cent was progressing, of 18 per cent improving; the condition of the rest was unknown. Of the entire 1000 patients, nearly 60 per cent were able to carry on a normal physical life 10 years after the disease began, and the number with severe disease was "indeed small." But the mortality rate of 24 per cent was "distressing."

In another excellent study from the same hospital Bland and Jones noted 306 deaths among 1500 cases of juvenile rheumatic carditis seen during the past 16 years. Causes of death in the 306 fatal cases were as follows: "rheumatic fever and congestive failure" in 205 cases, "rheumatic fever" (alone) in 24 cases, congestive failure in 21 cases; thus rheumatic fever itself was the direct or most important cause of death in a total of 250 cases (82 per cent). Death was due to bacterial endocarditis in 18 cases (6 per cent; acute in 4, subacute in 14 cases), to other causes related to the heart in 9 cases (3 per cent; sudden death in 6, cerebral embolus in 3 cases), to causes unrelated to the heart in 16 cases (5 per cent) and to unknown causes in 13 cases (4 per cent). In the 250 fatal cases of rheumatic fever, 23 per cent of the patients died the first year of the disease, 11 per cent more the second, and 13 per cent more the third year (a total of 47 per cent within three years). Fifteen per cent lived two years more (total deaths within five years, 62 per cent); 85 per cent were dead by the tenth year; 10 per cent lived from 11 to 15 years, and 3 per cent had had the disease at least 16 years before they died. For the remaining 2 per cent the duration of the disease at death was unknown. Obviously the first three to five years of the disease are the most critical. The patient's age (up to 15 years) at the onset of this disease was not a significant factor as far as subsequent longevity was concerned. The terminal picture of rheumatic fever differed notably from that of the earlier phases, and frequently resembled pneumonia, acute nephritis or uncomplicated carditis. Arthritis was not a feature of the fatal illness in any case, chorea in only two cases, nodules in 49 cases, carditis in all cases. Details of the various clinical features were given.

From such studies as these the prognosis for rheumatic patients with obvious carditis has been fairly well established. Not so well established is the outlook for patients who have had one or more rheumatic attacks but still present signs of a normal heart, or at most an apical systolic murmur. Boone and Levine studied 225 such cases of "potential rheumatic heart disease" over an average period of 9.6 years: mitral or aortic valvulitis developed subsequently in only 4.8 per cent. Thus if a patient survived one attack of rheumatic fever or chorea without obvious carditis developing, he had a 96 per cent chance of escaping valvulitis during the next five years. Of the patients surviving the attack with only an apical systolic murmur called

"mitral insufficiency," the condition of 58 per cent remained unchanged, 42 per cent subsequently had frank mitral stenosis or aortic insufficiency.

### ETIOLOGY AND PATHOGENESIS OF RHEUMATIC FEVER

*Factor of Infection.* Useful general discussions on the probable relationship of infection to rheumatic fever were published by Gibson,<sup>358</sup> Goldie, and Poynton.<sup>770</sup>

1. Nasopharyngeal infections. Green<sup>385</sup> cultured the throats of 200 patients with acute rheumatic fever and of 200 nonrheumatic controls. Antecedent throat infections had affected 78 per cent of the rheumatic, 46 per cent of the controls. Hemolytic streptococci were recovered in 58 per cent (116) of the rheumatic cases, in only 30 per cent (59) of the nonrheumatic cases. Streptococci in the rheumatic group were Lancefield Group A in 87, B in 3, C in 5, G in 5 per cent, D, E, F and H in none; in the nonrheumatic group they were Group A in 42, B in 15, C in 27, D in 2 per cent, E and F in none, G in 11 and H in 3 per cent of cases with positive cultures. Thus Group A hemolytic streptococci were recovered in 51 per cent of the total rheumatic cases, but in only 13 per cent of the total nonrheumatic cases. Such data suggest again a relationship between these bacteria and rheumatic fever.

In 1934 Long and Bliss recovered from the throats of normal and diseased humans "minute" beta hemolytic streptococci different from "ordinary" beta hemolytic streptococci. Further studies were reported.<sup>594</sup> From the throats of normal persons such "minute" streptococci were recovered by occasional throat cultures in 12 per cent, by repeated cultures in 23 per cent, of cases. They were found rarely in throats of persons ill with a variety of acute and chronic diseases (including scarlet fever, tonsillitis, acute upper respiratory infection) but frequently in cases of diffuse glomerular nephritis of type A (acute onset preceded by acute streptococcal infection) and in 55 per cent of 146 cases of rheumatic fever or carditis. "Ordinary" beta hemolytic streptococci were found in only 30 per cent of the 146 cases. Although both groups of hemolytic streptococci were recovered frequently from rheumatic patients, the minute variety occurred with notable preponderance in those more actively diseased.

2. Blood cultures. A review of studies from 1891 on the bacteriology of the blood in rheumatic fever was made by Leslie and Spence. By the technic used in their hospital, pathogenic organisms had never been recovered (during a period of 10 years) from the blood of normal persons, or patients without definite signs of disease, nor from rheumatic patients unless they had proved subacute bacterial endocarditis. To determine whether they had been missing significant organisms, a more elaborate method for blood cultures was devised, involving a primary culture and several subcultures. Cultures were made in 26 cases of active rheumatic fever. In all cases, primary cultures were negative (after 48 hours' incubation). In 11 of the

26 cases, all subcultures remained negative. In 14 cases, a variety of non-pathogenic organisms was found; in only one case was a pathogenic organism found. The organisms in these 15 cases were considered to be airborne contaminants, as results in controls were similar. Similar negative results were noted in four cases of chorea.

3. Skin tests. Positive skin reactions to extracts of hemolytic streptococci were noted by Goldie in 77 per cent of 80 rheumatic cases and in only 32 per cent of controls. The reaction usually became positive about the second or third week of illness except in severe cases when its appearance was delayed weeks or even months. Only 27 per cent of the rheumatic cases were skin-sensitive to *Streptococcus viridans*. Of Green's<sup>386</sup> 105 patients with acute and subacute rheumatic fever, 75 per cent gave positive skin reactions to a stock hemolytic streptococcal endotoxin as compared with 24 per cent of 105 nonrheumatic controls. The percentage of reactions to hemolytic streptococcal exotoxin was about equal in the rheumatic and control groups. Of 32 cases of acute rheumatism, 27, 14 and 13 respectively showed skin sensitivity to endotoxins of autogenous hemolytic streptococci, *Streptococcus viridans* and indifferent streptococci. In certain quiescent cases, rheumatic activity was induced by subcutaneous injections of hemolytic streptococcal endotoxin. Admittedly, the significance of these positive tests is not clear, but Goldie regarded them as an indication of local immunity to bacterial endotoxin, and an index of the circulating anti-endotoxin. At any rate, they seem to indicate a close connection between such bacteria and rheumatic fever.

4. Agglutination tests. Hemolytic streptococcal agglutinins have been found in high titer in the blood of patients with rheumatic fever by some (Coburn and Pauli, 1932) but not by others.<sup>4</sup> Of Goldie's 31 cases, in 16 (51 per cent) agglutination at a titer of 1 in 200 or over was found.

5. Precipitin tests. No new studies were reported.

6. Antifibrinolysins. No new studies were reported.

7. Antistreptolysins. In 37 of 50 rheumatic cases (but in no controls) Goldie found titers of over 200 Todd units. Considering 120 units as the upper limit of normal Koerner and Poulton found elevated values (125 to 400 units) in five cases of acute rheumatic fever.

*Factor of Bacterial Allergy.* Goldie interpreted the aforementioned findings as evidence that rheumatic fever (and also atrophic arthritis) results from sensitization to hemolytic streptococci. Wolffe and Digilio also accepted the idea of bacterial allergy as the cause of the disease. Gibson agreed that under Von Pirquet's broad conception of allergy (an altered capacity for reacting) "rheumatism comes into the ambit of allergy," but primarily rheumatic fever is an infectious process and to place its phenomena in the same category with those of asthma and hay fever "appears to afford no help in their explanation." Aschoff also concluded that allergic reactions occur in rheumatic fever, but "to maintain that rheumatism and allergy are equivalent is fundamentally impossible." During this infectious

disease, as in tuberculosis, allergic phases will intervene, but allergy does not play the chief part, according to Aschoff. The disease is undoubtedly caused by an undiscovered specific bacterium. "The therapy of the physician must, however, never be directed against the allergic phase, but against the true infecting bacteria. The entry of an infectious disease into an allergic phase only shows us a morphological peculiarity in the response of the tissue to the irritation of the disease. To combat the latter should ever be our task."

*Virus Theory.* Virus-like bodies were found in various exudates from cases of rheumatic fever by Schlesinger, Signy and Amies (1935) and by Eagles, Evans, Keith and Fisher. They seemed to be particularly significant because they were generally agglutinated by the patient's serum. These workers themselves insisted that the isolation of particles resembling elementary bodies, and even their agglutination by appropriate sera, are not proof that a virus is present or that it is the cause of the disease. Such particles must be proved to possess infectivity, and be able to produce the disease or at least some constant pathologic reaction in animals. In an attempt to prove their infectivity, inoculations thereof were given intratracheally, intravenously, into peritoneum, pericardium, muscles and joints of monkeys, hens, rats, and mice (Eagles, Evans, Keith and Fisher; Schlesinger and Signy). In some cases streptococci and streptococcal products were injected simultaneously to note whether symbiosis was present.<sup>261</sup> All the animal experiments gave essentially negative results. No endocarditis or pericarditis was produced. Noted were certain perivascular collections of cells in the myocardium, only superficially resembling Aschoff bodies, and certain other myocardial reactions considered to be nonspecific. Either the "elementary bodies" which were isolated are not the cause of rheumatic fever, or this disease, to which no known animal is susceptible, cannot be artificially produced by simple inoculation.

[These physicians deserve much commendation for their careful work. Investigating a "new" and intriguing idea, and having apparently obtained preliminary "successes," they nonetheless continued to appraise their own work very critically, and have only made conclusions which their work, not their hopes, would sustain. Their investigations should be continued and extended.—Ed.]

*Vitamin Deficiency.* Further evidence was given that a vitamin C deficiency commonly exists in rheumatic fever both during the active and quiescent stages.

Rinehart and his colleagues noted normal amounts of vitamin C (average 0.7 to 0.9; optimal levels at or above 0.9 mg. per 100 c.c. of plasma) in normal and non-rheumatic controls, low amounts (average 0.3; range 0.11 to 0.68 mg.; 97 per cent of cases below 0.5 mg.) in 30 cases of acute rheumatic fever and also in 22 inactive cases (average 0.38; range 0.10 to 1.20 mg.; 78 per cent of cases below 0.5 mg.). Sherwood also noted low concentrations (0.24 to 0.77 mg.) in five cases. Kaiser noted concentrations of vitamin C (per 100 c.c. of blood) ranging from 0.5 to 1.0 mg., in 125 normal controls, 0.57 to 0.9 in 25 acute or quiescent rheumatic cases. Values were

lower in the acute than in the quiescent cases. In some of the latter, values were normal. As rheumatic patients improved, the concentration of vitamin C in their blood improved. Nonrheumatic sick children also possessed values of vitamin C in the blood nearly as low as those of the rheumatic patients.

Keith and Hickmans performed vitamin C saturation tests on rheumatic children. They were given 500 mg. of vitamin C as a test dose; if 50 mg. were excreted within 24 hours, the patient was considered normal. The average output (24 hours) in 18 acute cases was 22 mg., that of 31 convalescent patients 12 mg. Children with acute disease excreted more than convalescent patients; the latter excreted amounts equal to those of controls of similar age. Saturation tests revealed a slight deficiency in the stores of vitamin in acute cases, as compared to convalescent cases or controls. Sodium salicylate with sodium bicarbonate, and fever reactions from typhoid vaccine produced slight increases in the excretion of vitamin C in the rheumatic cases.

The interpretation of these various data is difficult. Either most rheumatic patients are simply on a deficient diet, or the disease depletes their blood of the vitamin, or the deficiency represents an inherent or acquired metabolic fault which may be an integral factor in the cause of the disease. Rinehart and his colleagues again favored the latter idea, that vitamin C deficiency is a non-specific predisposing factor. Kaiser did not regard the deficiency as due solely to inadequate diets, but felt it impossible to say whether it preceded and disposed to the disease, or resulted from it. Keith and Hickmans and Sherwood considered the deficiency a result, not the cause, of the disease.

*Conclusions on Etiology.* Reviewing various theories on etiology, Poynton<sup>770</sup> restated reasons for his dissatisfaction with the theory of bacterial allergy and for his belief in the idea that the disease represents a bacterial infection of unknown type (probably streptococcal) which spreads generally from nasopharynx, via the blood stream (but not by mass invasion) to affect distant tissues. Gibson also reviewed current ideas and stated, "Obviously no conclusion is possible at this stage. Each theory which has been put forward conflicts to a greater or less extent with the available evidence. The problem may be restated, but not answered."

[To this conclusion we certainly agree.—Ed.]

#### TREATMENT OF RHEUMATIC FEVER

There have been no outstanding new developments in treatment.

*Rest.* This remains the "sheet anchor" of treatment.<sup>857</sup> The first consideration is to provide absolute rest in bed with the patient in the position of maximal comfort, supported by pillows as necessary.<sup>1001</sup> Even if no carditis is evident, the minimal period of rest in bed should be one month. No change in the application of absolute rest should be made until there have been normal pulse, temperature, sedimentation rate, and no change in cardiac size and murmurs for at least six weeks. The patient then is permitted to increase his activity gradually through 5 or 6 grades (schedules given) of increased activity (Sheldon; Warner). This may take six months or more.

*Salicylates.* Amounts prescribed must be adequate. Daily doses advocated were 60 to 100 grains for children,<sup>857, 1001</sup> 150 to 200 grains for young adults, given with equal or double amounts of sodium bicarbonate. In two or three days, when symptoms begin to lessen, the doses of salicylates should be reduced, then continued for two to three weeks. If, after a satisfactory initial response from salicylates, the temperature rises again, either the dose of salicylates was reduced too rapidly, or carditis may be developing, for fever from carditis is scarcely affected by salicylates. Only rarely is it necessary to give salicylates intramuscularly or intravenously (daily for three to four days in doses of 1 grain in 1 c.c. of water for each year of the child's age; Warner). "It cannot be too strongly urged that if [salicylates in the doses noted] do not control the joint pains and pyrexia within 48 hours, it is probable that the diagnosis must be revised."

Salicyl salicylate (salysal) was preferred to sodium salicylate by Litchfield because it is practically tasteless, less toxic and equally effective in doses half that for sodium salicylate, but it reduces fever more slowly. The annoying sweating which often accompanies salicylate therapy may be controlled by the oral administration of 5 to 10 grains of camphoric acid given one hour before the anticipated seizure of sweating.<sup>581</sup>

[We have never used this.—Ed.]

*Sulfanilamide.* Despite the supposed relationship between hemolytic streptococci and rheumatic fever, sulfanilamide seems to have no beneficial effect on the course of any of the manifestations of rheumatic fever. Swift, Moen and Hirst gave about 3 to 4 gm. of the drug daily for four or five days to eight patients with chronic recurring rheumatic fever; larger amounts could not be given, and marked toxic effects were produced (increased fever, tachycardia). No benefits were noted; indeed, the rheumatic manifestations were intensified. The formation of antistreptolysins was uninfluenced by the drug. Disappointing results were also noted by Massell and Jones, who gave the drug (about 6 to 7 grains daily per 10 pounds of body weight) to 58 patients: 16 were moderately or severely ill, 25 were convalescents, 17 had inactive disease, including seven with chorea. The course of the disease was unaffected. Toxic reactions occurred frequently, especially severe fever; hence the use of the drug is "contraindicated in the presence of active rheumatic fever." In an unstated number of cases (no details given) Sheldon and Simmons and Dunn found the drug valueless, except that two cases of "rheumatic pneumonia" became afebrile. Moore gave the drug to three patients with rheumatic fever: two recovered, one died (no details).

[Sulfanilamide may prove more useful in the prevention of rheumatic exacerbations precipitated by acute hemolytic streptococcal pharyngitis than in the treatment of acute rheumatic fever. Following the oral use of neoprontosil by Herrell and Brown, throat cultures became negative in 10 of 16 carriers of hemolytic streptococci. Of special interest are the current studies (1939) of Thomas and France and of Coburn and Moore. The latter gave 30 grains of sulfanilamide daily from November



to June inclusive to 80 rheumatic children: 79 escaped hemolytic streptococcal infection and signs of rheumatic activity. Thomas and France gave 15 to 20 grains of the drug daily from November to June inclusive to 30 rheumatic patients; 30 control rheumatic patients received no drug. Major attacks of rheumatic fever affected none of those receiving the drug and four of the controls; acute beta hemolytic streptococcal infections affected none of those given the drug and at least one of the controls. No significant drug toxicity was noted by either group of investigators.—Ed.]

*Other Drugs.* An opportunity to prevent the expected rheumatic flare-up would surely seem to be afforded by the interval of one to four weeks which generally exists between acute nasopharyngitis and the subsequent rheumatic exacerbation, but so far little has been accomplished in this direction. Sheldon prescribed 20 to 30 grains of acetylsalicylic acid (aspirin) daily during the sore throat and for some time afterward in an attempt to prevent or mitigate the impending rheumatic exacerbation. With similar intent, Schlesinger prescribed aspirin daily for four weeks after the nasopharyngitis and believed that by this means the number of relapses and the mortality were definitely reduced. Among 27 patients given aspirin thus, 21 recovered, 6 died; mortality was 22 per cent. Among 24 patients not so treated 13 recovered, 11 died; mortality 45 per cent.

[Similar studies of larger numbers of children might give different results. Others do not support the idea that the use of salicylates will prevent rheumatic relapses. But it may mask some symptoms, e.g., fever and joint pains. Nobody has yet noted whether the use of aspirin daily during winter months would be a more effective prophylactic than its intermittent use only after acute nasopharyngitis, or whether results from aspirin would compare with those from the use of sulfanilamide given daily throughout the winter.—Ed.]

Results from the use of aminopyrine (initial doses 30 grains daily) in 10 cases of active rheumatic fever with carditis were "extremely gratifying" to Heninger and McHardy. All symptoms, including fever, tachycardia, leukocytosis, abnormal erythrocyte sedimentation rate, and joint pains, were promptly relieved, presumably also those of active carditis.

[The follow-up time was not long enough to note the eventual effect on carditis. Aminopyrine has been known to be as effective as salicylates in controlling fever and joint pains, and smaller doses than those of salicylates can be successfully used, but previous workers at the Rockefeller Institute and elsewhere, after treating large series of cases, have discontinued its use because of the fear of agranulocytosis and because it had no effect on the course of carditis.—Ed.]

*Removal of Tonsils.* Allan and Baylor noted subsequent recrudescences in only 44 per cent of 108 "rheumatic patients" (36 with acute polyarthritis, 46 with chorea, 16 with polyarthritis and chorea, 10 with rheumatic carditis alone) subjected to removal of tonsils and adenoids. Carditis subsequently affected only a few of those not so affected at the time of operation; hence, removal of tonsils and adenoids was recommended. Turnley also advocated tonsillectomy for all rheumatic patients if their general condition permits. He reviewed results in 3,172 cases of "rheumatism": since the latter included many varieties of "indefinite" pains, acute rheumatism

and chronic arthritis without differentiation, his statistics are of no significance. The operation is rarely fatal; out of 65,253 tonsillectomies, death occurred only six times: from hemophilia, pneumonia, heat prostration, ether narcosis, acute edema of thymus, status lymphaticus, and never from hemorrhage directly.

Meakins deplored the "perfect passion" for tonsillectomy in rheumatic fever, and considered tonsillectomy immediately thereafter "the epitome of fanaticism." After studying 150 cases, Archer concluded that tonsillectomy did not prevent or modify initial or subsequent rheumatic attacks. A post-operative exacerbation of rheumatic fever "directly" after tonsillectomy occurred in two cases. Tonsils should be removed only if they are obviously diseased or persistently harbor hemolytic streptococci, and then only when the rheumatic process has subsided (Ash; Warner). Having studied the effect of tonsillectomy on 521 rheumatic children (425 with and 96 without their tonsils at the time of the initial rheumatic attack) Ash also concluded that, whether done before or after an initial rheumatic attack, tonsillectomy did not influence the subsequent appearance or seriousness of carditis.

*Vaccines; Serums.* Wolffe and Digilio noted "encouraging results" (no details given) from the use of autogenous vaccines of bacteria to which patients' skins were sensitive. A stock filtrate of hemolytic streptococci was used by Wasson in an attempt to "immunize" 34 rheumatic children against subsequent attacks. Acute exacerbations affected only 6 per cent (2) of those so treated and 29 per cent (19) of 66 untreated controls. Reviewing similar studies, Warner concluded that vaccines of hemolytic streptococci and other organisms have proved of little value, and there is no reliable evidence to countenance their intravenous use. Vaccines have generally not increased immunity as measured by antibodies or decreased hypersensitivity as shown by skin tests. In doses used they have not prevented sore throats or rheumatic relapses. According to Warner, no one has apparently used smaller doses absorbed by slower methods: he stated that it may be worth while to study the effect of small doses given subcutaneously or orally.

Intramuscular injections of antiscarlatinal serum (Eason and Carpenter 1937) in acute cases unresponsive to salicylates were cautiously approved.<sup>857, 1002</sup> Friedman, Klein, and Rosenblum noted no effect from intravenous injections of convalescent serum into four patients with active rheumatic fever, or of serum from actively ill patients into four convalescent patients. But when serum was drawn from 11 actively ill patients, kept 33 to 86 days, and reinjected into the same patients during convalescence, in six of seven cases symptoms and signs "suggestive of the original disease" were reproduced (slight increases in pulse rate, slight fever—never over 101° F.).

[Reactions were not striking and occurred 3 to 11 days after injections. Joint pains occurred in only two cases, joint swelling only once. Perhaps the reactions were nonspecific in type.—Ed.]

*Diet and Vitamins.* Despite the fact that the blood of most rheumatic patients is somewhat deficient in vitamin C,<sup>806</sup> no notable effects from ad-

ministration of vitamin C were reported, with the possible exception of those in Mosse's case, that of a Chinaman with acute rheumatic fever who "responded dramatically" to the use of vitamin C (contained in a daily ration of 800 to 1200 c.c. of "fresh red fruit juice"). [Details of the case are meager and confusing. One cannot determine from the dates given how long the disease antedated treatment or how long symptoms continued thereafter.—Ed.] According to Kaiser vitamin C will not prevent or cure the disease. The deficiency is probably not the cause, but the result of this infection as it is of many infections. Nevertheless, the increased need of the rheumatic patients for vitamin C should be recognized, and generous amounts of fruit juices or vitamin C supplements should be prescribed.<sup>135, 523, 860</sup> To rheumatic children cod liver oil (2 drams) in tomato juice (1 ounce) was given twice daily by Bacal and Struthers.

*Fever Therapy.* Fever therapy seemed to reduce symptoms and shorten attacks in 15 cases of acute rheumatic fever (Dunn and Simmons). Several patients, previously unrelieved by other forms of therapy, noted marked relief of symptoms after the first session of fever. In three cases recurrences occurred within two weeks to 21 months. [Several fever sessions were generally given, each at intervals of four to seven days. Hence enough time elapsed for natural remissions to have occurred. No attempt was made to evaluate such therapy in preventing or moderating carditis.—Ed.] Osborne, Blatt and Neymann gave fever therapy to seven patients with carditis and chorea and to five with carditis alone. It did not harm the heart; in the first group cardiac "improvement" was sometimes noted as evidenced by improved electrocardiograms and disappearing systolic murmurs; in the second group, only one patient really improved. Ferderber noted "improvement" (not defined) in most of his patients with rheumatic fever or rheumatic carditis given fever therapy.

[None of those who have reported beneficial effects from fever therapy for rheumatic fever and carditis have followed up the cases long enough to note whether the course of the carditis has really been affected.—Ed.]

*Special Treatment for the Heart.* Small doses (3 to 6 minims) of digitalis were prescribed by Warner in an attempt to slow the hearts of affected children. [This is not easy to do even with large doses. Most authorities consider digitalis of value in carditis only in the presence of cardiac failure.—Ed.] Graded plans for resumption of physical activity were outlined.<sup>41, 341, 857, 1002</sup>

*Institutional Care and Climate.* Certain physicians believe that, whenever economic status permits, rheumatic children should be taken south to avoid the cold storms of winter and spring. Choice American climates are, according to Mills, the southern parts of New Mexico, Arizona, and California. Mills recommended the migration of such patients well south, preferably near the Mexican border from El Paso west, rather than to southern Florida, or the West Indies where tropical storms and long debilitating summer heat might lessen the chance for complete quiescence of the disease. Migration should be permanent, not for the winter alone. For children of parents who cannot afford the cost, convalescent camps or farms

should be established by the government in choice southwestern spots. "The total burden on public funds would probably be no more than is required by their frequent and prolonged stays in northern hospitals at high overhead costs." In such convalescent homes, problems peculiar to the disease could be studied more carefully. To date the number of such convalescent homes in the United States is so few, and the waiting list for them so long, that months may elapse before the sick child can gain admittance. Swift contrasted the inadequate existing provisions for cardiac patients with those for the tuberculous: for the latter there are in the United States and its possessions 749 institutions with 92,786 beds, and an additional 5,000 under construction. This includes 78 federal, 399 state, county and municipal, and 71 private or semiprivate institutions.

[No figures for beds available for convalescent rheumatic patients were given, but admittedly the number is very inadequate.—Ed.]

Schemes for managing a rheumatism pavilion in Montreal (Bacal and Struthers) and a convalescent cardiac school at Caldwell, New Jersey (Kaufman) were described. Some physicians<sup>5</sup> consider the psychologic effect of special schools bad for rheumatic children, but as a result of his study of the emotional and social development of 21 adolescent girls with rheumatic carditis Silver strongly opposed this view. Psychic disturbances of such children arise not because of their own knowledge of their disability and the limitation it imposes, but from other causes: parental overprotectiveness, "sense of guilt," and evidences that the community considers the child handicapped. The emotional and social difficulties engendered thereby can best be eliminated by adjustments in special residential schools for rheumatic children. Unquestionably, the greatest strides in the development of special rheumatism units, convalescent hospitals, and cardiac schools have been made in England<sup>773, 344</sup>: synopses of these valuable schemes were outlined by Furniss, Glover, and Schlesinger. In London alone provisions have been made for the special care of 1100 convalescent rheumatic children. By such care the mortality at West Wickham was reduced to 12 per cent, as compared to that of 26 per cent in other parts of Great Britain. The provision of 1.7 convalescent beds for each 1000 elementary school children was considered necessary in London.<sup>365</sup>

*Prophylaxis.* Important points in the prophylaxis of the disease are improvement of living conditions for children (proper housing, clothing, and feeding; slum clearance, development of more playing fields), careful removal of infected foci, frequent examination of school children, and special care for rheumatic suspects. Public health nurses, teachers and mothers each play an indispensable rôle in this scheme.<sup>32, 234</sup>

#### SYDENHAM'S CHOREA

*Clinical Data.* The clinical features of chorea were briefly reviewed.<sup>636</sup> Lueth found basal metabolic rates to be normal in 42 juvenile cases of acute Sydenham's chorea, regardless of its severity. The mental changes present

in 35 cases of chorea minor were grouped by Shaskan: group 1, 10 cases of chorea and severe psychosis (two with carditis); group 2, nine cases of chorea with mild mental disturbances (behavior problems, etc.); group 3, 16 cases of chorea with gross mental changes. In the milder uncomplicated cases, there were no serious disturbances in thinking or in orientation, but behavior problems were sometimes serious. In the severe cases, the hyperkinesia or akinesia influenced thinking. Hallucinations and delusions were often present. In the more severe cases, confusion and disorientation were present. Severe mental symptoms were a grave prognostic sign and were seen in older patients. Of the 8 patients without carditis in group 1, 4 died.

*Pathogenesis; Relationship to Rheumatic Fever.* From the time of Bright, a close relationship has generally been thought to exist between chorea and rheumatic fever, although Osler noted such a relationship in only 21 per cent of his cases of chorea. Neither bacteriology nor pathology has solved the relationship. According to some, no structures resembling rheumatic nodules have been seen in the few cases of pure chorea which have come to necropsy (McCulloch); according to others, perivascular nodules resembling Aschoff bodies have been noted in the brains of patients dead of chorea (Schroder). "If the patient with chorea dies, he dies of rheumatism or its complications. The question still remains whether he can have chorea without rheumatism." The conclusion of current writers would seem to be that generally he cannot.<sup>980, 979</sup>

Among 1052 rheumatic patients studied by Sutton and Dodge, chorea was present at some time in 467, absent in 585. Emotional upsets were less frequent precipitants of chorea than recent infections, especially of the rheumatic variety. The choreic children exhibited no particular personality or body type, and had "normal" or "dull normal" intelligence quotients similar to controls. Of the 467 choreic patients, 91 (about 20 per cent) had "pure chorea" (no associated rheumatic manifestations), 133 (28 per cent) had muscle and joint pains, 243 (52 per cent) had frank rheumatic attacks. At the end of 4.8 years (mean) of observation, organic carditis was found to affect 19 per cent of those who had pure chorea, 30 per cent of those with muscle and joint pains, and 73 per cent of those who had had frank rheumatic attacks (also 72 per cent of the 585 rheumatic patients who had not had chorea). Therefore Sutton and Dodge concluded that chorea must be considered not only a manifestation, but a major manifestation, of rheumatic infection. Although chorea per se is not usually a serious disease, the child who begins his rheumatic career with chorea runs a 50 per cent chance of carditis developing, a 75 per cent chance of some noncardiac rheumatic symptoms developing.

A study by Usher led to somewhat similar conclusions. Of 105 patients with chorea, on admission 56 gave a history of "pure chorea," but 27 per cent of them were found to have carditis, generally mild; 49 gave a history of chorea and other rheumatic symptoms; in these cases of "mixed chorea" carditis, often of notable severity, had developed in 65 per cent.

To stress its relationship to rheumatic fever, McCulloch spoke of chorea minor as "encephalitis rheumatica," presumably an exudative manifestation similar to that in joints, heart and elsewhere. Schroder also speculated as to whether the true cause of chorea might not be an allergic reaction, perhaps a localized edema, in the brain itself, probably in the lenticular nuclei, resulting from selective action of a rheumatic virus.

*Treatment.* Contrary to the view of Sutton and Dodge, focal removal seemed less important to Usher than the control of psychic trauma: he prescribed daily 45 grains of calcium gluconate and 15 grains of aspirin generally for three to four weeks to control the chorea. Sulfanilamide given for two to four weeks by Massell and Jones had no effect in seven cases of chorea.

Fever therapy continued to be the therapeutic method of choice. It was not of benefit in Shaskan's cases of chorea with severe psychosis, but was "helpful" for patients with minor mental symptoms or with behavior problems. Schmidt treated 15 patients with artificial fever; the condition of many had been resistant to fever from typhoid vaccine: 10 were promptly cured, two "improved," two did not improve, and one patient died (no further details). Osborne and his colleagues<sup>733, 735</sup> again reviewed their favorable results reported previously. Choreic patients of Ferderber<sup>300</sup> who received only five or six fever sessions (each three hours at 105 to 106° F.) became symptom free but relapsed after four to six months; those who received 8 or 10 treatments were cured of the chorea; complicating carditis was not harmed. A follow-up study by Sutton and Dodge<sup>929</sup> on the condition of 99 children given fever therapy as compared to 66 treated otherwise indicated that in the former group thereafter polyarthritis developed much less frequently, carditis and recurrent chorea somewhat less frequently. The mortality of the former group was also significantly lowered.

Of 48 treated and 23 untreated patients, observed one to three years, chorea subsequently developed in 32 and 38 per cent, polyarthritis in six and 32 per cent, carditis in 13 and 26 per cent, fatal carditis in three and 13 per cent respectively. Of 51 treated and 37 untreated patients observed four to six years, chorea subsequently developed in 41 and 51 per cent, polyarthritis in six and 33 per cent, carditis in 29 and 35 per cent, and fatal carditis in 2 and 11 per cent respectively. Aortic lesions developed in only one of the 99 treated cases, in seven of the 60 untreated cases.

[If subsequent work confirms these results the modification of associated or impending carditis would appear to be a more important effect of fever therapy in cases of chorea than the shortening of the chorea itself.—Ed.]

Usher alone seemed disappointed with fever therapy: to him fever induced by typhoid vaccine or by inductothermy seemed too drastic and not certainly preventive of recurring chorea.

# CASE REPORTS

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## ADRENAL HEMORRHAGE WITH PURPURA AND SEPTICEMIA (WATERHOUSE FRIDERICHSEN SYNDROME) WITH RECOVERY; CASE REPORT \*

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ADRENAL hemorrhage complicating septicemia is rarely suspected during life. Almost invariably it is a postmortem discovery, but usually when found it can be correlated with the clinical picture and implicated as an important factor in causing the death of the patient. That it is probably more common than realized is indicated by the admission of three cases to the University Hospital within one year. Two of these have been reported by Sacks,<sup>1</sup> who in a review of the literature found only 64 cases published before 1937. The third case is described in this report; recovery of the patient prevented proof of the diagnosis by autopsy.

The reports of Waterhouse<sup>2</sup> in 1911 and Friderichsen<sup>3</sup> in 1918 have given the name of the "Waterhouse-Friderichsen syndrome" to fulminating septicemia with purpura and adrenal hemorrhage. Since Sacks' report Magnussen<sup>4</sup> has published one and Simpson<sup>5</sup> two cases.

When the descriptions are detailed all cases show a striking similarity. Aegerter<sup>6</sup> and Sacks<sup>1</sup> have called attention to this. The patient is usually a child who has become suddenly ill during the course of what is, apparently, a mild respiratory infection. Vomiting, chills and fever occur, followed by collapse within a few hours. The blood pressure, when estimated, is said to be low, though few definite figures are given. Fever is usually high or remittent, but early death has precluded more than a few determinations in each case. Cyanosis is common, and with the accelerated respiratory rate, this feature may lead to a diagnosis of pneumonia. Within 12 hours after onset a petechial rash is observed on the skin; the lesions increase in size and number, and in a few hours ecchymoses 10 to 30 mm. in diameter, or even larger, may be present. The leukocyte count is usually high. Even in those cases caused by meningococcic septicemia, typical physical signs of meningitis are usually not seen, but resistance to passive movement of the extremities, headache and weakness are common, and in Aegerter's review convulsions were noted in 12 of 57 cases. Death occurs usually within 24 hours after onset.

The illness is so fulminating and death so early that complete studies are usually not done, and only after autopsy are the symptoms correlated with the characteristic pathology. Aegerter suggested studies of sodium metabolism and recommended treatment with large doses of cortical adrenal extract, sodium chloride and epinephrine. There are in the literature no reports of serum sodium

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and potassium determinations, and no reports of treatment of the syndrome by these measures.

Of the 57 cases reviewed by Aegerter 55 were examined post mortem. Bilateral adrenal hemorrhage was found in 52 and unilateral hemorrhage in three autopsies. Sacks' and Simpson's cases had bilateral hemorrhage. The glands may be completely disorganized by gross bleeding or multiple minute areas of hemorrhage may be found. Microscopic examination shows hemorrhage of variable extent, often with complete disruption and extensive necrosis of the gland.

When bacteriologic study is done the meningococcus is usually discovered to be the infecting organism, but in other instances the pneumococcus, hemolytic streptococcus and staphylococcus have been recovered by blood culture.

#### CASE REPORT

The patient, F.R., was a white woman, aged 27, married, whose health had been generally good until the onset of her illness. On February 2, 1937, she contracted an acute cold with cough and profuse nasal discharge, but was well enough to continue her usual duties. During the afternoon of February 8 she had several chills and vomited. About 10:00 p.m. she felt weak and somewhat short of breath. Her physician was called and though he advised hospitalization it was refused. During the night she was restless and did not sleep. At 8:00 a.m. on February 9, pneumonia was suspected by her physician and at 9:30 a.m. she was admitted to the University Hospital where she remained until 1 p.m. February 10, 1937.

On admission to the University Hospital her temperature was 103.6° F. (rectal), pulse 120, respiration 12. Examination revealed a young woman, semicomatose, but easily aroused to a moderate degree of consciousness. The lips, ears and finger-tips were cyanotic. Respiration was shallow. Scattered over the body, especially on the forearms and antecubital fossae, were many small petechiae from 0.5 to 2.0 mm. in diameter. The pupils were small and active; the fundi could not be seen through the undilated pupils. The eardrums, mouth and throat were negative. The lungs were apparently normal, though examination was not entirely satisfactory. The heart was normal in size and position, with clear, distant, rapid and regular sounds. The blood pressure was 65 systolic and 35 diastolic. The abdomen was soft. No tenderness could be elicited on deep pressure in the costovertebral angles or in the upper abdomen anteriorly. The extremities were negative. There was no stiffness of the neck and Kernig's sign was only suggestively positive, probably because the patient resented passive motion of her extremities. The deep reflexes were moderately hyperactive and no pathological reflexes could be elicited.

As soon as the hypotension was discovered 1 c.c. of 1:1000 epinephrine was given subcutaneously without demonstrable effect. Oxygen by nasal catheter slightly decreased the degree of cyanosis. Attempted carbon dioxide hyperventilation increased the rate and depth of respiration, lessened cyanosis, and caused a rise of blood pressure to 85 systolic and 40 diastolic. The blood pressure returned to its original level when carbon dioxide was temporarily discontinued.

Hypodermoclysis of physiological sodium chloride solution was started at 11:00 a.m., February 9, with 1 c.c. of epinephrine added to each liter. After 200 c.c. had been absorbed blood was drawn for serum sodium and potassium determination. Sodium was reported as 147.7 milliequivalents per liter and potassium as 3.04 milliequivalents, both normal values. Fifty grams of dextrose in 500 c.c. of 0.8 per cent sodium chloride were given intravenously at 12:30 p.m.

Lumbar puncture was performed at 10:30 a.m. The fluid was clear, and the pressure was not measured. The cell count was reported as 21 per cu. mm. with 99



per cent polymorphonuclears and 1 per cent lymphocytes. A trace of globulin was present. No bacteria were seen on direct examination, but culture was reported on February 10 as showing *Neisseria intracellularis*, agglutinated by antimeningococcic serum in dilution of 1:1280. Blood culture produced the same organism.

The patient did not void during her stay in the hospital. Her blood non-protein nitrogen was 39 mg. per cent, sugar 126 mg. per cent, and CO<sub>2</sub> was 42 volumes per cent. The leukocyte count on February 9 was 8,950, with a differential formula of polymorphonuclears 88 per cent, lymphocytes 8 per cent and monocytes 4 per cent. The erythrocyte count was 4.25 million and hemoglobin 13 grams (Sahli). On February 10 the leukocyte count had increased to 22,480.

As the clinical picture was identical with that described in those patients showing massive adrenal hemorrhage at autopsy, it was decided to treat the patient with cortical adrenal extract and continue with the supportive measures noted above. Accordingly, she was given 10 c.c. of cortical adrenal extract (Parke Davis & Co.) intramuscularly at 1:15 p.m. on February 9. One c.c. of epinephrine solution was given at 4:00 p.m., followed by 10 c.c. of cortical adrenal extract (Upjohn) intravenously and 10 c.c. intramuscularly at 5:00 p.m. and again at 10:00 p.m.

During the afternoon of February 9 the patient's condition was somewhat improved, with less evidence of collapse. Her blood pressure was 85 systolic and 55 diastolic at 1:00 and 2:00 p.m., falling to 64 systolic with uncertain diastolic pressure at three o'clock. After epinephrine administration it rose to 84 systolic and 60 diastolic. The temperature varied from 105° F. to 106° F. until 10:00 p.m., then ranged from 100° F. to 101.4° F. until transfer. The heart rate continued between 130 and 140. The respiratory rate increased to 30-35 after 2:00 p.m. During the afternoon restless delirium replaced the apathetic semicoma. The purpuric spots increased rapidly in size and number, and spread over the trunk and extremities. Many of the lesions were from 1 to 3 cm. in diameter, irregular and sharply defined. The skin became ecchymotic where it was traumatized by needles.

At 9:00 p.m. February 9, though cultures of blood and cerebrospinal fluid had not been reported, treatment for meningococcic septicemia was initiated. Antimeningococcic serum was given intravenously at 9:00 p.m. and intramuscularly at 2:00 a.m. February 10, and at the latter time subcutaneous administration of 2.4 gm. of sulfanilamide was started. Intravenous administration of 500 c.c. of 0.8 per cent sodium chloride was carried out between 2:00 and 2:30 a.m.

On the morning of February 10 the patient's general condition was improved and her appearance was more suggestive of epidemic meningitis. The neck was slightly stiff, but Kernig's sign was still doubtful. Cyanosis had disappeared. Occasional muscular twitching was noted, but there were no convulsions. The mental state was unchanged. Blood pressure was 104 systolic and 70 diastolic. When the bacteriologic studies were reported she was transferred at 1:00 p.m. to Sydenham Hospital, the municipal contagious disease hospital of Baltimore City.

At Sydenham Hospital lumbar puncture was done at 4:00 p.m. Thirty c.c. of cloudy cerebrospinal fluid were removed and 30 c.c. of antimeningococcic serum replaced. The cerebrospinal fluid cell count was 5200, with 89 per cent polymorphonuclear leukocytes. *Neisseria intracellularis* were found on direct examination and grown on culture.

On February 11, 30 c.c. of serum were given intrathecally, 30 c.c. intravenously, and 5.5 gm. of sulfanilamide orally. On February 12, 45 c.c., on February 13, 15 c.c., and on February 14, 20 c.c. of serum were given intrathecally. Sulfanilamide was given orally in dosage of 1.3 gm. on February 13 and 2.6 gm. on February 16. No serum was given after February 14, but sulfanilamide was continued by mouth until February 25, with an average daily dose of 4.5 gm.

The cerebrospinal fluid was sterile after February 11. The patient's general condition began to improve on February 14. There was no recurrence of the shock and prostration. The temperature finally became normal on February 25, when the cerebrospinal fluid was clear, with 11 cells per cu. mm. Convalescence was complicated by a left corneal ulcer thought to be herpetic in origin. On discharge, March 7, blood pressure was 138 systolic and 80 diastolic.

Final examination was made on July 14, 1937. At that time the patient felt very well but convalescence had been slow, as recovery was not complete until late in May. Physical examination was negative except for slight scarring of the left cornea, minimal ectropion of the left lid with loss of lashes, and a soft systolic murmur at the apex of the heart transmitted a short distance toward the axilla. Blood pressure was 130 systolic and 75 diastolic while lying down and 140 systolic and 90 diastolic while sitting.

The characteristic appearance of this patient, which agreed fully with clinical descriptions of the Waterhouse-Friderichsen syndrome, probably justifies the diagnosis of adrenal hemorrhage at the onset of the meningococcic infection. Diagnosis of the syndrome cannot be certain without autopsy. Aegerter<sup>6</sup> suggested studies of sodium metabolism, but these studies require determination of sodium balance, evidently impossible in such an acute illness. Loeb, Atchley, Benedict and Leland<sup>7</sup> reported that the average reduction of blood serum sodium was as little as 2.3 milliequivalents per day after total adrenalectomy. Certainly in an illness of only 12 hours' duration one could not expect the blood sodium level to be appreciably affected. Even in Addison's disease the blood serum sodium may be within normal limits, and the abnormality of sodium metabolism only discoverable by comparison of blood level and urinary excretion during balance studies.<sup>8</sup>

The many therapeutic procedures employed in this case increase the difficulty of estimating the effectiveness of the attempted specific treatment with cortical adrenal extract. It is even possible, though unreported, that spontaneous recovery may occur in meningococcic septicemia with adrenal hemorrhage. However, the unexpected recovery of this patient from the severe initial collapse, possibly as the result of the treatment outlined, suggests the use of similar measures when the diagnosis of adrenal hemorrhage is suspected.

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## SUPPURATIVE ARTHRITIS DUE TO A HEMOLYTIC STREPTOCOCCUS OF THE LANCEFIELD GROUP B; A CASE REPORT \*

By LOWELL A. RANTZ, M.D., *Boston, Massachusetts*

LANCEFIELD<sup>1</sup> has described a method for the differentiation of the hemolytic streptococci into groups by means of the precipitin reaction, based on the presence in this organism of a group specific carbohydrate obtainable by acid hydrolysis. She has pointed out, and the observation has been confirmed by others, that streptococci etiologically involved in practically all cases of human infection are representatives of her group A. With Hare<sup>2</sup> she studied a large number of cases of puerperal sepsis and demonstrated organisms of this group in 45 of 46 cases of severe infection, the other being caused by a member of group G. In seven cases of mild infection, organisms of group B were cultured from the vagina. No other instances of infection with streptococci of the latter group appear to have been reported except three fatal cases of puerperal sepsis by Fry,<sup>3</sup> in which the striking features were the presence of endocarditis in two, and the tendency to localized abscess formation in the other.

It is the purpose of this report to describe a case of suppurative arthritis in which a streptococcus of group B was the etiological agent.

### CASE REPORT

A 53 year old, colored, domestic worker entered the fourth medical service of the Boston City Hospital on August 14, 1938, with a complaint of pain and swelling of the left knee and hand for five days. Family history was non-contributory, as was past history except for moderate dyspnea on exertion for one year. Ten days before her admission to the hospital six teeth had been extracted. Four days later she felt very weak and chilly, and vomited. The next day pain and swelling appeared in her left knee and hand, gradually increasing in severity until the day of entry. At that time physical examination revealed a well-developed, obese, colored female who was acutely ill. The temperature was 100.5° F.; the pulse rate 100. Examination of the head and neck was negative. The chest was clear, the heart enlarged, and the blood pressure 190 systolic and 100 diastolic. No organs or masses were palpated in the abdomen, but a hard, irregular mass was felt in the uterus on pelvic examination. Over the third and fourth left metacarpo-phalangeal joints and about the left knee there was tenderness, swelling, redness, and abnormal warmth, with limited and very painful movement in the affected joints.

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Laboratory examinations revealed a normal urine; a hemoglobin of 75 per cent Sahli, 4,000,000 red blood cells, and 10,000 white blood cells, with a differential count of 72 per cent polymorphonuclears, 17 per cent lymphocytes, 10 per cent monocytes, and 1 per cent basophiles. The Hinton and gonococcal complement fixation tests were negative. Culture of the blood was sterile. The blood uric acid was 2.2 mg. per 100 milliliters. The electrocardiogram showed left ventricular preponderance.

A diagnosis of hypertensive cardiovascular disease, fibromyomata uteri, and infectious arthritis of undetermined etiology was entertained at this time. Paracentesis of the knee was performed and 25 milliliters of thin, cloudy fluid containing 38,000 cells per cubic millimeter, all of which were polymorphonuclears, were removed, and a pure culture of weakly hemolytic streptococci was grown from it.

Following the last observation she was transferred to the sixth surgical service for orthopedic management. The course of her illness during her hospital stay is illustrated in chart 1.

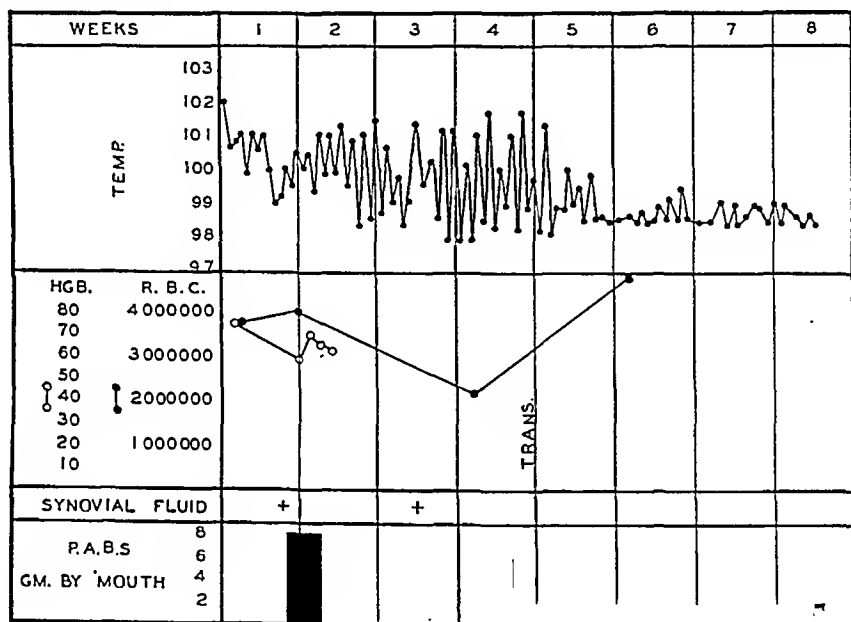


CHART I.

The temperature was of remittent type for five weeks, at which time it returned to normal by lysis. The knee was tapped again on September 6 and, when a similar streptococcus was found, sulfanilamide, in a dose of two grams daily, was begun and continued until September 27. Eight grams had been given previously on August 20 and 21. The affected limb was constantly immobilized from September 8 until the time of discharge by means of a plaster cast covering the entire leg. Anemia developing during the course of the illness necessitated a transfusion of 500 c.c. of whole blood on September 15. In other respects her course was prolonged but uneventful. The affected joints of the left hand subsided within two weeks without special therapy. At the time of discharge from the hospital she felt well and returned to her own home where immobilization of the limb in plaster for another three months was planned, eventual complete healing with ankylosis of the joint being anticipated.

#### BACTERIOLOGY

The majority of the strains of hemolytic streptococci of the Lancefield group B have been isolated from the mastitis of cows, from milk, and from milk

products. Certain cultural and biochemical characteristics have been described for this group. Sodium hippurate is reduced, growth occurs on 40 per cent bile agar, a final pH of 4.4 to 4.5 is reached in glucose broth, and trehalose is fermented, but not sorbitol.<sup>1</sup> Tillett and Garner<sup>4</sup> have demonstrated the failure of these organisms to produce fibrinolysin.

The biochemical, serological, and cultural characteristics of the organism, KB1J, isolated from the infected knee, as described in this report, are listed in table 1. Similar studies with K17A4 a known strain from group A, V9 a group

TABLE I

Strain	Sero- logical Group	Reduction of Sodium Hippurate	Final pH Glucose Broth	Growth on Bile Agar		Fermentation Trehalose	Fermentation Sorbitol	Fibrinolysin
				40 per cent	10 per cent			
K17A4	A	—	4.9	—	+	+++	—	++
KB1J	B	++++	4.2	++++	++++	+++	—	—
V9	B	++++	4.6	++++	++++	+++	—	—
K64	C	—	4.9	—	—	—	—	—

B strain, and K64 a group C strain are included. From these observations it is possible to state definitely that this streptococcus is a member of group B. On 5 per cent blood agar surface colonies are large, flat, smooth, and gray, surrounded by a small area of partial hemolysis, quite unlike the usual small dome-shaped white colony with wide band of hemolysis that is so characteristic of the ordinary hemolytic streptococcus isolated from human sources. The other strain of this group mentioned above has a similar colonial appearance.

#### COMMENT

Only a few cases of serious infection in man have been reported in which streptococci of the Lancefield group B have been demonstrated to be the etiological agent. In the present case it is of interest to speculate as to the means by which an organism, ordinarily of such weak invasive qualities, reached the joints in this patient. No definite conclusions are to be drawn, but it should be noted that four days before the onset of her illness six teeth were extracted from her mouth, and it seems fair to postulate that the natural body defenses were broken down in this area, allowing a few organisms to penetrate the tissues. A transient bacteremia very likely occurred, with a focalization of bacteria in the affected joints. The relatively mild course suggests that the streptococci of this group are not as destructive as most of the members of group A.

Little specific information is available in regard to the action of sulfanilamide in infections due to group B streptococci. However, Bauer and Gunderson<sup>5</sup> treated four cases of bovine mastitis, a disease of cattle usually caused by organisms of this group, with this drug, and demonstrated in one instance a disappearance of the organisms from the milk during its administration and in three others a reduction of the total number of organisms. Long, Bliss and Feinstone<sup>6</sup> have mentioned its use in infections of the urinary tract caused by members of this group and suggest urinary levels of the drug of 250 to 300

mg. per 100 milliliters, but they have presented no other clinical data. The dosage of sulfanilamide in the case presented here was so small that it seems unlikely that it exerted more than a very slight effect on the course of the illness, but it probably exerted some inhibitory action on the growth of the organisms, and thus may have aided the natural antibody mechanism to sterilize the joint.

It is probable that practically all infections in man due to the hemolytic streptococcus are caused by members of Lancefield's group A. Since routine grouping of the strains isolated in medical and surgical practice is rarely done, no accurate statistical evidence is available. It is quite likely that, if this procedure were carried out, many more instances of infection by organisms of other groups would be discovered and the etiology of certain atypical cases clarified.

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#### METASTATIC CARCINOMA SIMULATING HYPERPARATHYROIDISM \*

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THE clinical syndrome of hyperparathyroidism has been established. The literature contains many articles by competent investigators giving the salient features of this disease with the requisites for diagnosis. Since surgical intervention, especially early in the disease, may result in cure, it is important that physicians should bear this condition in mind, especially when bone pain or pathologic fracture, with roentgenologic findings of decalcification of the skeleton are present. An essential diagnostic feature of hyperparathyroidism is an elevation of blood calcium, usually to above 12 mg. per 100 c.c.

The presence of hypercalcemia even to a marked degree does not invariably mean hyperparathyroidism. Hypercalcemia can be induced by injection of para-

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thormone, or by large doses of vitamin D or of dihydrotachysterol. Also, hypercalcemia is frequently found in cases of multiple myeloma when the level of the serum protein is elevated. In 1931, Mason and Warren<sup>1</sup> reported a case of a woman, aged 48, with metastatic carcinoma from the breast which simulated hyperparathyroidism. The presence of a high level of blood calcium, varying between 12.9 and 17.6 mg. on 11 determinations, led to some difficulty in the diagnosis of their case. Boyd,<sup>2</sup> in his book on pathology, mentions two cases of metastatic carcinoma with widespread decalcification of the bone and high blood calcium determinations. One had a primary malignant lesion of the breast and the other a bronchiogenic carcinoma. Gutman, Tyson and Gutman<sup>3</sup> have also mentioned the association of metastatic carcinoma with high blood calcium. We wish to add a case which is almost a duplicate of that of Mason and Warren, especially in the matter of a marked elevation of blood calcium.

### CASE REPORT

A girl of 20 years was referred to the clinic with a diagnosis of suspected hyperparathyroidism. She had been in excellent health, attending college, and leading an active life up to 10 months previously, when she began to complain of severe low backache. She had lost some 12 pounds (120 to 108 pounds) during the two years before the onset of this back discomfort, but this was attributed to over-activity. The backache continued practically unchanged for five months after which she began to complain of more or less continuous pains in the legs. At that time it was thought she was suffering from rheumatic fever. Although the pains were not localized to particular joints, the severity of the discomfort and the presence of a low grade fever suggested this diagnosis. From this time on the patient was bedridden and her course was progressively downhill. Pain in the bones and joints became generalized so that motion caused great distress. Rapid weight loss of 30 pounds occurred to the time of admission. In the last six to seven weeks nausea and vomiting had been troublesome symptoms.

Physical examination revealed that the patient was thin and markedly emaciated, with a dry and shiny skin. The pulse rate was 100, the temperature normal, and the blood pressure 140 mm. of mercury systolic and 90 mm. diastolic. The muscles were markedly atrophied with loss of tone. Movement of the arms and especially of the legs produced severe pain in the lower back and shoulders. The legs were kept in a semiflexed position. No abnormalities of the bones could be found on palpation. The right breast was movable but uniformly firm and nodular. The left breast was soft and flabby. No nodes were felt. There was a scar, 10 cm. in length, over the right lower lateral chest wall from a recent rib resection.

The laboratory studies revealed that the urine contained considerable albumin and many leukocytes. The specific gravity was normal. The hemoglobin was 47 per cent (Sahli); erythrocytes numbered 2,750,000 and leukocytes, 10,350 per cubic millimeter of blood. The value for the nonprotein nitrogen was 46 mg. per 100 c.c. of blood. In the table are given the levels of the serum calcium, phosphorus and phosphatase over the course of one month. A test for Bence-Jones protein was reported as negative and the serum protein was 6.5 gm. per 100 c.c.

Roentgenologic studies of the bones, including the spine, ribs, pelvis and skull, showed a diffuse mottling type of decreased density. The ilia were more extensively involved in this process than the other bones of the skeleton, as shown in figure 1. The lung fields showed a faint, diffuse, snowflake type of mottling. Roentgenologic study of the gastrointestinal tract was reported as negative. A roentgenogram of the



FIG. 1. Extensive involvement of the ilia can be seen.

abdomen revealed a small area of increased density opposite the edge of the third lumbar vertebra in the region of the left ureter.

The case presented an interesting diagnostic problem. In favor of hyperparathyroidism was the clinical course, having as the outstanding factors bone pain, hypercalcemia, and the diffuse structural change shown by the roentgenograms of the bones.



In addition, a shadow in the region of the left ureter suggested the presence of a stone, which would favor the above diagnosis. Multiple myeloma seemed to be ruled out by the normal value for serum protein and the absence of Bence-Jones protein in the



FIG. 2. Specimen from the rib. A border of cortical bone has been partially eroded by tumor. The bone marrow and trabeculae have been replaced almost completely by fibrous marrow containing small alveoli and ill-defined epithelial cells, showing some vascularization and in places having distinct lumina in the cell masses. Rare mitoses are present ( $\times 200$ ).

urine. However, close scrutiny of the roentgenograms of the skeleton revealed the fact that decalcification was not the outstanding feature, but that diffuse bone destruction played the initial rôle. Beginning compression fractures in two dorsal vertebrae seemed to point to metastatic disease. Therefore, malignancy had to be ruled out before surgical exploration of the neck for a parathyroid tumor could be considered.

In the course of a careful physical examination, one of us (C. B. K.) had noted some abnormality in the right breast which had not been previously observed. To approach the problem, a portion of the breast was removed for biopsy and the specimen of the

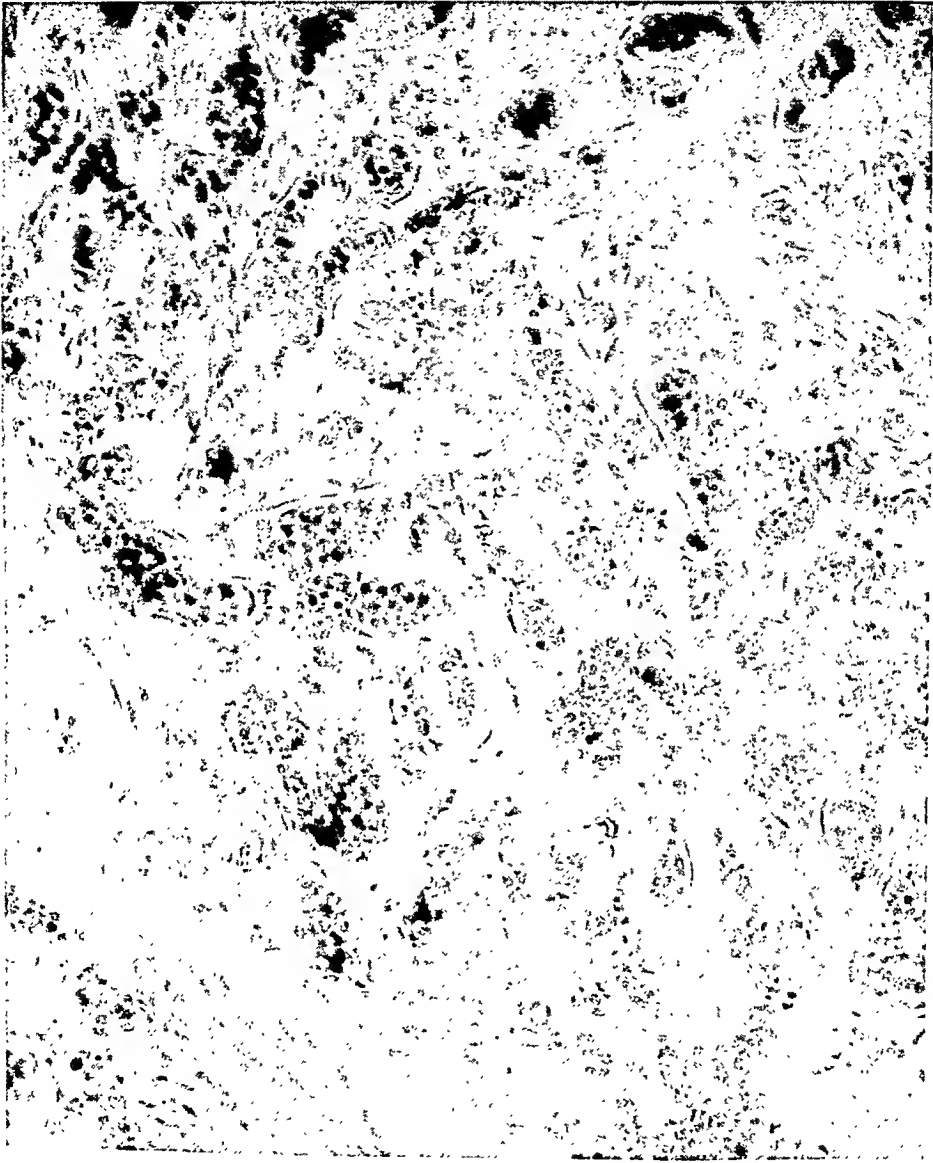


FIG. 3. The breast tissue has been completely replaced by large and small masses of compact, epithelial cells, with occasional mitotic figures. The stroma is moderately abundant. Both small blood vessels and lymphatics have been invaded by the tumor masses. There is slight variation in size of the epithelial cells. Mitoses are present but relatively few. A number of the cells contain traces of secretion ( $\times 200$ ).

rib which had been removed elsewhere was procured. After study of the slides,\* a diagnosis was made of carcinoma simplex of the breast with metastasis to the bony skeleton (figures 2 and 3).

\* We wish to acknowledge the assistance of Dr. Shields Warren for his aid in studying the slides.

## COMMENT

This case apparently is the second to be reported in which metastatic carcinoma produced a marked elevation in the serum calcium. In the case of Mason and Warren, extensive generalized bone changes were observed, with resultant collapse of dorsal vertebral bodies similar to that observed in our case. Just as extensive changes occurred in our case in that every part of the skeleton of which roentgenograms were taken was found to be involved. Apparently the myriads of bone metastases acted through pressure or irritation to produce decalcification of adjacent bone tissue, flooding the blood stream with calcium. As a result, the level for serum calcium was substantially elevated. To produce such an increase in serum calcium there must of necessity be widespread osseous encroachment.

Ducuing<sup>4</sup> has recently emphasized the frequency with which carcinoma of the breast gives rise to osseous metastases. He described a type of bone pain

TABLE I  
Serum Calcium, Phosphorus and Phosphatase

Date	Calcium, mg.	Phosphorus, mg.	Phosphatase, Bodansky units
7-19	14.9		
7-23	15.2		
8- 2	16.3		
8- 9	17.9		
8-25	15.4	3.1	4.6

associated with diffuse metastasis from the breast which had an abrupt onset in the form of "rheumatismal" crises. This is of interest since rheumatic fever was suspected early in our patient's illness. This type of symptomatic response is rare because usually the clinical picture in metastatic disease is that of localized involvement with the severest suffering associated with one region.

## CONCLUSION

A case is reported of mammary carcinoma, which had produced generalized osseous metastasis, in a girl of 20 years. The diagnosis was at first confused with hyperparathyroidism because of a uniformly elevated value for serum calcium.

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## EDITORIAL

### THE INEFFICIENT TREATMENT OF ANEMIA

The studies of the past fifteen years have added greatly to our knowledge of the various types of anemia and have provided a sound basis for their intelligent and efficient treatment. As yet, however, there has not been a corresponding improvement in the methods of treatment generally employed.

Most cases of anemia can be placed in one of three large groups, depending upon the relative size and hemoglobin concentration of the red cells. The hypochromic microcytic group, with small pale cells, is associated with iron deficiency. This anemia practically always responds to the administration of adequate doses of simple inorganic iron salts. Whole liver may be of benefit as a food, particularly as a source of proteins and vitamins and, secondarily, of iron. The various liver extracts, however, have not proved to be of any practical value. The second, hyperchromic macrocytic group has cells which are larger and darker than normal. The anemia is owing to a lack of the erythrocyte maturing factor, and responds to liver, and to potent liver extracts or stomach preparations. The cases in the third group, which is quite heterogeneous, have cells which *on the average* are within normal limits as to size and hemoglobin content. The anemias of this type are due to a great variety of causes such as acute and chronic infections, chemical poisons, cancer, and various other chronic debilitating diseases. Successful treatment depends upon finding and eliminating the cause of the anemia. Neither iron nor liver preparations are of any material benefit.

Manifestly individual exceptions to this classification occur. Thus some cases of leukemia and of refractory anemias may show macrocytosis and hyperchromia and yet fail to respond to liver extract. In special cases dietary deficiencies other than a lack of iron—particularly a lack of proteins or of vitamins B and C—may cause an anemia which is resistant to treatment unless the diet is rendered adequate. Such cases are relatively uncommon, and require special treatment.

If this knowledge is to be used effectively so that the patient receives the type of treatment he requires with a minimum of unnecessary medication, a precise diagnosis must be made. At a very minimum it is necessary to determine whether the anemia is hypochromic, hyperchromic or normochromic in type. This necessitates a reasonably accurate determination of both the hemoglobin and the red cell count, procedures which are in no way difficult but do require a moderate amount of practice for accurate performance.

It is very difficult to determine directly what proportion of physicians in active practice actually utilize these methods of diagnosis and guide their treatment accordingly. A survey of the advertisements of remedies for anemia distributed to physicians by the leading pharmaceutical houses would seem to indicate that their use must be the exception rather than the rule.

The great majority of such preparations are "shot-gun" mixtures of two or more ingredients. Most of them contain iron and liver extract (erythrocyte maturing factor) in some form, or stomach concentrates. A few contain "secondary anemia liver extract"; many, vitamin supplements—brewer's yeast, B<sub>2</sub> complex, thiamin chloride, riboflavin, ascorbic acid. A few contain copper, and an occasional one, some other metal such as cobalt, manganese or arsenic.

More than a hundred different preparations of this type have been advertised to the medical profession within the past year or two, and if one may judge by the volume of advertising, at least 25 to 30 of them must be "large sellers." In the case of one of the most popular preparations the gross retail sales are reputed to be about three million dollars a year.

In most of these preparations the ingredients are doubtless therapeutically active and if given in a dose large enough to supply a sufficient quantity of the particular material needed they will ordinarily yield satisfactory results. The huge volume in which these preparations are now consumed, however, is less a tribute to their potency than to the clever way in which they have been advertised and promoted.

First of all, they appeal directly to those physicians who can not make blood examinations themselves and are unwilling to refer patients to others for this purpose. A circular advertising one such preparation states that it is designed for the oral treatment of all types of anemia which respond to liver therapy or the administration of iron salts. It "may be used advantageously when facilities for determining the nature of an anemia are temporarily not available or diagnosis must for other reasons be delayed."

Failure to make a precise diagnosis is particularly unfortunate in patients with anemia. In cases of anemia secondary to infection or to other organic disease, such shot-gun therapy will be futile. The underlying cause must be found and eliminated. Even in conditions such as pernicious anemia and idiopathic hypochromic anemia in which specific replacement therapy is all that is now available, a positive diagnosis is almost as essential. Without it few will persist in maintaining indefinitely a course of treatment which at best is tedious and involves an expense which is burdensome for the average patient.

In the second place, advertisers have capitalized to the utmost such statements as they can find in the literature to bolster their claim as to the advantages of such combinations. The evidence for the effectiveness of "secondary anemia liver extract" is derived almost exclusively from animal experiments. Most of the reports of its use in man indicate that it is of little, if any, demonstrable value. Much the same is true of the effect of copper. The alleged adjuvant effect of ordinary liver extract in treating hypochromic anemia is also open to serious doubt. Statements can be found in articles by several eminent hematologists in favor of this claim and these statements have been quoted extensively by the manufacturers. Precise data to support such claims are sparse, however, and they appear to be based largely on

general impressions. Furthermore, they are at variance with the experience of the majority of observers, which indicates that in most cases of hypochromic anemia liver extract is superfluous if not entirely useless. Cases with a double deficiency do undoubtedly occur, but they are relatively rare, and merit individual attention.

There are two other practical objections to the general use of such shot-gun preparations. In many of them the amount of one of the ingredients is relatively small, and to get an effective quantity of it, a disproportionately large and correspondingly expensive dose of the preparation must be wasted. Secondly, it involves an unnecessary expense to the patient to pay for the superfluous ingredients in such a preparation, merely to save his doctor the trouble of ascertaining and indicating which one is really needed.

The addition of a trace of copper to an iron preparation need involve no appreciable additional expense. This is largely true also of the addition of ferrous sulphate or ferrous carbonate to liver extract intended for patients with pernicious anemia, although both are usually superfluous. Excessive cost becomes important, however, if unnecessary vitamin preparations are added, or if such mixtures are to be used for patients with hypochromic anemia. The ingredients which are superfluous for them account for most of the cost. Furthermore, the cases of hypochromic anemia vastly outnumber those with pernicious anemia and related types, and the total wastage is correspondingly multiplied.

The extent of this exploitation may be appreciated from a comparison of the cost of the quantity of some of these preparations which is required to provide an optimal but not excessive dose of iron. Thus, the retail cost of a daily dose of 0.8 gm. of ferrous sulphate should not exceed about four cents a day. This alone is ample for the great majority of cases of hypochromic anemia. The cost of a similar dose of iron in the form of shot-gun preparations varies greatly, but ranges from about sixteen cents to forty cents a day for a number of these most extensively used. In some cases it is much higher, reaching \$1.00 to \$1.50 a day in the case of some preparations containing iron in less utilizable form. Such quantities, however, are probably never actually administered. The growing use of these preparations at least has probably reduced the employment of the practically inert and extravagant parenteral injections of iron.

For those patients who need them, liver extract or vitamin supplements should be prescribed freely. An excess cost for drugs alone of from \$3.60 to \$10.80 a month, however, is a tax on the patient which is not justifiable when it benefits only an exceptional case. The cost of an accurate blood examination will be covered quickly by the savings it makes possible, and at the same time treatment can be established on a logical basis. This is one field in which the cost of medical care can be materially and advantageously reduced.

P. C.

## REVIEWS

*A Biological Approach to the Problem of Abnormal Behavior.* By MILTON HARRINGTON, M.D. 459 pages; 16 × 23.5 cm. The Science Press Printing Company, Lancaster, Pa. 1938.

The author devotes the 454 pages of text to the establishment of two theses: (1) That the most useful view of behavior is purely mechanistic; and (2) that psychoanalytic theory is inadequate. Both theses are tenable and it is no doubt justifiable to attempt to prove both, except that both tasks have been executed much better elsewhere. Perhaps the author's error lies in trying to think in two directions at once. Perhaps it lies in inadequate preparation for the effort. At any rate, one finds him arguing almost entirely from analogy instead of demonstrations within the field of the material under consideration—a procedure which is of dubious propriety. He cites hypothetical cases instead of observed instances of behavior, a method which enables him to create situations to suit his needs instead of holding him to fact. In the few instances where he uses observed case material, he is much less didactic and comes much closer to an adequate statement. In dealing with the emotions, he is superficial and seems unaware of, or ignores, many of the recent advances in this field. Here he resorts to the nothing-else-but type of argument, the validity of which one must always suspect. (Page 197) "Reactions to those things that have previously occasioned pain, to which we apply the term 'fear,' are then, it would appear, due to the reactivation of the pain mechanism. In short, fear is anticipatory pain." . . . "Similarly, what we call 'hope' is in reality anticipatory pleasure." (Page 223) "This feeling of fear, it would appear, is merely pain plus the sensations arising from the bodily reaction of suspense," etc.

Moreover, while condemning the conception of conscious phenomena (desire, wish, will, etc.) as activators of behavior, he nevertheless finds it quite impossible to proceed without these terms used in this exact sense. (Page 35) "The fact of the matter is, of course, that the bulk of mankind, who cling to the doctrine of animism with such great emotional intensity, do so from motives which have little, if anything, to do with its value as a means of explaining or correlating facts. Of these motives, the strongest is, in all probability, the desire for survival." He justifies this use of terms by saying that when he uses them he really means the physiological processes underlying them. This may be true, of course, but then neither he nor anyone else knows what these processes are.

One occasionally encounters more serious contradictions within the text, of which the author seems unaware. His discussion of the "pleasure mechanism" is peculiarly confusing in this respect.

Because the author attempts to introduce new concepts, inadequately founded and of dubious utility; and since your reviewer believes that even a valid concept cannot be established by the author's method, it seems impossible to recommend this work to students as it could only lead to confusion in a field where order is just beginning to emerge.

L. F. W.

*Architecture of the Kidney in Chronic Bright's Disease.* By JEAN OLIVER, Professor of Pathology, Long Island College of Medicine, Pathologist, The Hoagland Laboratory. 257 pages; 20 × 29 cm.; with 112 illustrations, including 5 color and 39 aquatone plates. Paul B. Hoeber, Inc. 1939. Price, \$10.00.

This book presents an amplification and extension of work begun in 1930, the progress of which appeared in the *Archives of Pathology* during 1933, 1934 and 1935. It represents a painstaking piece of work on which the author is to be complimented.

This investigation is based on the method of microdissection of blocks of kidney from cases of Bright's disease and recording the architectural units by camera ludica drawings and stereograms. The author has judiciously separated his objective findings from his elaborations and at the end of each chapter there is interpretative comment.

The material in this investigation consists of 23 cases previously studied from both the clinical and pathological standpoints and reported by Addis and Oliver in 1931. The majority of these cases were clinically diagnosed hemorrhagic Bright's disease (glomerulo-nephritis), but there are also included cases of the arteriosclerotic variety, degenerative pyogenic form and the amyloid kidney.

The alterations of the nephron, the transformation of the arterial system and the general alterations in kidney parenchyma are objectively worked out in each condition.

This study only emphasizes the fact that whether the process is primarily characterized by glomerular inflammation, amyloid infiltration or arteriosclerosis, each end with an organ of similar architectural pattern. One outstanding fact has been brought to light about which there has apparently been a misconception. This is that a tubule does not atrophy as a result of destruction of its glomerulus. Direct, newly formed vascular branches are demonstrated in great numbers in these contracted kidneys, connecting the afferent arteriole of the glomerulus with the intertubular capillaries.

This structural evidence, to the author's mind, compels the conclusion that there has been an excretory shift toward the tubular side, and that the circulation of blood in these contracted organs has changed from a primarily glomerular distribution to a direct tubular supply. The correlation of this rearranged function is left largely to the reader.

This book is of special interest only to those scientifically interested in the somewhat confused problem of chronic Bright's disease. It fills no particular need as far as the average physician is concerned.

C. G. W.

*The Distribution of the Leukocytes in the Vascular System.* By GERT VEJLENS. 239 pages. Almqvist and Wiksells Boktryckeri A.-B. Upsala, 1938.

This small volume, published originally as Supplement XXXIII in 1938 in the *Acta Pathologica et Microbiologica Scandinavica*, is an inaugural dissertation presented by the author for the degree of doctor of medicine at the University of Upsala. The work, carried out under the direction of Professor Fahreus, represents an effort to determine the leukocyte distribution in the vascular system under varying physiological and pathological conditions. Looking upon the leukocytes as particles suspended in a flowing liquid medium, the author attempted to study the effect of alterations in the viscosity of the fluid, changes in the velocity of flow, and the influence of vessel diameter on the white cell count. Hydrodynamic principles are called upon liberally to explain many of the observed phenomena. The experiments have been carefully planned and the results evaluated statistically in many instances. The observations are summarized and an extensive bibliography is appended. Very little in the way of clinical application has been attempted and the work therefore has a limited immediate value for the general reader.

M. S. S.

*The Vaginal Diaphragm; Its Fitting and Use in Contraceptive Technique.* By LEMON CLARK, M.S., M.D. 106 pages. C. V. Mosby Co. 1939.

This monograph deals with only one method of contraception, i.e., the use of the vaginal diaphragm. The book contains 106 pages and 53 fine illustrations, consisting



of diagrams and pictures of wax models showing the proper fitting of the diaphragm in various normal and pathological pelvic conditions. It also contains a discussion of the various types of diaphragms and methods of fitting and inserting them, together with the indications and contra-indications for the use of these various types of methods. The book is well written and covers the subject quite comprehensively.

J. C. D.

*Manual for Diabetic Patients.* By W. D. SANSUM, M.D., with ALFRED E. KOEHLER, M.D., Ph.D., and RUTH BOWDEN, B.S. 227 pages; 21 × 14 cm. The Macmillan Company, New York. 1939. Price, \$3.25.

This manual is written primarily for patients—"to make the patient as familiar as possible with his disorder."

Part one consists of fifteen short chapters. These chapters discuss diabetes in a style which is clear and concise. The discussion on Food Utilization proves the exception; it is too complex for the average patient to understand. The chapter on treatment with insulin is excellent and should overcome at the outset the fear and distrust with which many laymen regard this life saving medication. Adequate distribution of diet to more evenly match the action of modified insulin is advised.

Part two consists of a brief but well planned summary of practical diabetes as applied to diabetes. Forty pages are devoted to recipes. This reviewer welcomes the thirty-six recipes for desserts which are made possible by "adequate carbohydrate diets." It is obvious, however, that a dessert like pumpkin pie (C-28, P-12, F-24) would unbalance any but a high calorie diet. The book is recommended for patients, students and physicians.

L. P. G.

*Hydrophthalmia or Congenital Glaucoma.* By J. RINGLAND ANDERSON, M.C., M.D., B.S. (Melb.), F.R.C.S. (Edin.), F.R.A.C.S., D.O.M.S. (Lond.) 377 pages, 15.5 × 25 cm.; 116 illustrations. Cambridge University Press, London; Macmillan Co., New York. 1939. Price, 25 shillings; \$7.00.

In this monograph on congenital glaucoma, Dr. Anderson takes up the question of this rather unusual condition. He bases his study on the collected findings of 205 eyes in 116 patients, as a result of a questionnaire in which he included a report on a case studied by the reviewer. The monograph is perhaps the first comprehensive resumé of the subject to appear in English, for as Sir Herbert Parsons in the Foreword points out, the last work appeared in French in 1897 by Edmund L. Gros.

The first chapter is devoted to the question of definition and etiology. In this study, Dr. Anderson shows that boys are more frequently affected than girls. The age of onset is at or very soon after birth.

In Chapter II he discusses at some length the condition of megalocornea in distinction to hydrophthalmia. The former apparently is a reversion to a primitive mammalian condition and is not, in his opinion, glaucoma.

In Chapter III he takes up the development and comparative anatomy of the involved tissues. Certainly the developmental procedure is of vast importance since many believe that the condition is always the result of developmental defects, and while the comparative anatomy may be of interest, unless the animals which are studied are known to develop congenital glaucoma, it would hardly seem to throw much light upon the subject in the human.

Chapter IV deals with the pathology of congenital glaucoma. In this chapter he reproduces many of the illustrations showing the pathology in reported cases.

In Chapter V on pathogenesis, Dr. Anderson devotes some time to the developmental theory, the inflammatory theory, and the various other theories that have been

advanced. In his summary he states that 86 per cent are apparently results of abnormal development of the mesh-work of the angle.

The treatment taken up in Chapter VI gives a review of practically all cases reported and stresses the fact that medical treatment is of practically no avail and that surgical treatment to be of value should be performed in the first year.

In Chapter VII dealing with prognosis, the author states that the outlook is very grave. However, if the cases are operated upon early, apparently about 50 per cent retain vision for at least two years. As previously stated the earlier the operative procedure, the better hope for successful outcome.

Chapter VIII under General Reflections, outlines Dr. Anderson's previous findings.

Attached to a pocket on the back binder of the book are folders with tabulations of 113 specimens examined.

This monograph is undoubtedly a masterpiece upon the subject of a very limited field in ophthalmology, and will probably remain as an authority for many years.

C. A. C.

## COLLEGE NEWS NOTES

### NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. Edward L. Bortz, Philadelphia, Pa.  
Dr. Frederick L. Brown, New Brunswick, N. J.  
Dr. Walter R. Steiner, Hartford, Conn.  
Dr. Harry R. Ryan, Rutland, Vermont  
Dr. Charles H. Sprague, Boise, Idaho  
Dr. Lodovico Maneusi-Ungaro, Newark, N. J.

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### GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged:

Dr. David M. Baltzan, F.A.C.P., Saskatoon, Sask., Canada—9 reprints;  
Dr. John V. Barrow, F.A.C.P., Los Angeles, Calif.—2 reprints;  
Dr. Nathan Blumberg, F.A.C.P., Philadelphia, Pa.—1 reprint;  
Dr. Julius H. Comroe, Jr. (Associate), Philadelphia, Pa.—1 reprint;  
Dr. O. J. Farness (Associate), Tucson, Ariz.—2 reprints;  
Col. F. H. Foucar, (MC) U. S. A., F.A.C.P.—1 reprint;  
Dr. J. C. Geiger, F.A.C.P., San Francisco, Calif.—1 reprint;  
Dr. O. F. Hedley (Associate), Philadelphia, Pa.—13 reprints and 2 journals;  
Dr. Bert F. Keltz, F.A.C.P., Oklahoma City, Okla.—2 reprints;  
Dr. Kenneth R. McAlpin, F.A.C.P., New York, N. Y.—14 reprints;  
Dr. M. Hill Metz (Associate), Dallas, Texas—2 reprints;  
Dr. E. W. Phillips, F.A.C.P., Phoenix, Ariz.—2 reprints;  
Dr. William B. Rawls, F.A.C.P., New York, N. Y.—2 reprints;  
Dr. Rafael Rodriguez-Molina, F.A.C.P., San Juan, P. R.—1 reprint;  
Dr. J. K. Williams Wood (Associate), Troy, Pa.—1 reprint.

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### SPECIAL BOARD EXAMINATIONS

#### *American Board of Internal Medicine*

Oral examinations of the American Board of Internal Medicine will be given just previous to the meeting of the American College of Physicians in Cleveland, April 1-5, and just in advance of the A.M.A. Meeting in New York, June 10-14. Applicants who have passed the written examination and plan to take the oral examination in 1940 should advise the secretary at least six weeks in advance of the date of the examination they desire to take. Next written examination, October 21. Applications must be filed with the secretary by September 1. Secretary, Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

#### *American Board of Pathology*

The next meeting and examination of the American Board of Pathology will be held in New York, June 10-11, 1940. Application should be filed with the Secretary, Dr. F. W. Hartman, Henry Ford Hospital, Detroit.

## AMERICAN BOARD OF PEDIATRICS

The American Board of Pediatrics has announced the 1940 schedule of examinations as follows:

April 30 and May 1—New York, N. Y.

May 18—Kansas City, Mo.

June 1 and 2—Seattle, Wash.

November 16 and 17—Memphis, Tenn.

Application should be filed with the Secretary, Dr. C. A. Aldrich, 723 Elm St., Winnetka, Ill.

## AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

The next meeting and examination of the American Board of Psychiatry and Neurology will be held in Cincinnati, May 18-19, 1940. Application should be filed with the Secretary, Dr. Walter Freeman, 1028 Connecticut Ave., N.W., Washington, D. C.

## AMERICAN BOARD OF RADIOLOGY

The next meeting and examination of the American Board of Radiology will be held in New York, N. Y., June 7-10. Application should be filed with the Secretary, Dr. Byrl R. Kirklin, 102-110, Second Ave., S.W., Rochester, Minn.

## REGIONAL MEETING OF MONTANA MEMBERS

The annual meeting of the Montana Branch of the American College of Physicians, consisting of the Fellows and Associates of the College in the state, met at Great Falls on the afternoon and evening of February 17, 1940. Thirteen of the fifteen members and three guests were present. Officers elected for the ensuing year were: Dr. F. R. Schemm, F.A.C.P., president; Dr. A. R. Foss, F.A.C.P., vice-president; and Dr. Wayne Gordon (Associate), secretary-treasurer. The afternoon program consisted of clinical papers, in some instances with the presentation of the patients, by some of the members residing in Great Falls. The evening was devoted to dinner and to a series of scientific papers. The program included: Renal Dwarfism, Dr. A. L. Gleason, F.A.C.P., Great Falls; Encephalitis, Dr. C. F. Little, F.A.C.P., Great Falls; Angioneurotic Edema, Dr. A. C. Johnson (Associate), Great Falls; Recurrent Heart Failure, Dr. F. R. Schemm, F.A.C.P., Great Falls; Recent Observations on the Principles of Radiation Therapy in Carcinoma, Dr. E. D. Hitchcock, F.A.C.P., Great Falls; Peripheral Vascular Disease, Dr. M. D. Winter, F.A.C.P., Miles City; Hypoglycemia Complicating Diabetes Mellitus, Dr. Wayne Gordon (Associate), Billings; and Pariarteritis Nodosa, Dr. F. H. Crago (by invitation), Great Falls.

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On January 1, 1940, Dr. Lowell D. Snorf, F.A.C.P., was appointed Chief of the Medical Staff of the Evanston Hospital. Dr. Snorf succeeds Dr. James G. Carr, College Governor for Northern Illinois, who retired.

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Dr. Louis Faugeres Bishop, Jr., F.A.C.P., addressed the Cuban Society of Cardiology on the subject of "Heart Block," Friday, February 23, 1940, in Havana, Cuba.

Lieutenant Colonel James Stevens Simmons, (MC), U. S. A., F.A.C.P., who for the past three years has been on duty as Assistant Corps Area Surgeon at Headquarters, First Corps Area, Boston, Mass., was transferred on February 15 to the Professional Services Division of the Office of The Surgeon General, U. S. Army, Washington, D. C.

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Among the speakers who will address the Section on Gastro-enterology of The Medical Society of New Jersey at its 174th Annual Meeting, to be held at Atlantic City, June 4-6, 1940, will be the following:

Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, Pa.  
Dr. Clarence L. Andrews, F.A.C.P., Atlantic City, N. J.  
Dr. Charles L. Brown, F.A.C.P., Philadelphia, Pa.  
Dr. Herbert Thomas Kelly, F.A.C.P., Philadelphia, Pa.  
Dr. Manfred Kraemer, F.A.C.P., Newark, N. J.  
Dr. Thomas FitzHugh, Jr., F.A.C.P., Philadelphia, Pa.  
Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa.  
Dr. William A. Swalm, F.A.C.P., Philadelphia, Pa.  
Dr. L. M. Morrison (Associate), Philadelphia, Pa.  
Dr. C. C. Beling, F.A.C.P., Newark, N. J.  
Dr. David Ward Scanlan, F.A.C.P., Atlantic City, N. J.

A joint session of the Section on Medicine and the Section on Gastro-Enterology will be held Tuesday morning, June 4, 1940. Dr. Thomas M. Kain, F.A.C.P., of Camden, N. J., is chairman of the Section on Medicine; Dr. Hyman I. Goldstein (Associate), of Camden, N. J., is chairman of the Section on Gastro-Enterology.

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Dr. Fred M. Smith, F.A.C.P., Iowa City, Iowa, will participate in the annual session of the Idaho State Medical Association in Sun Valley, September 11-14, 1940.

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Dr. Maxwell Finland, F.A.C.P., Boston, Mass., and Dr. Josephine B. Neal, F.A.C.P., New York, N. Y., presented a symposium on the treatment of meningitis before the New England Pediatric Society, February 7, 1940.

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Dr. Ernest H. Gaither, F.A.C.P., Baltimore, Md., addressed the Section on Medicine and Pediatrics of the Academy of Medicine of Northern New Jersey, January 9, 1940, on "Modern Aspects of Peptic Ulcer Therapy."

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Dr. George Harlan Wells, F.A.C.P., Philadelphia, Pa., addressed the Atlantic County Medical Society of New Jersey on "Cause and Treatment of Congestive Heart Failure," January 12, 1940.

Dr. Conrad Wesselhoef, F.A.C.P., Boston, Mass., addressed the Medical Society of the County of Albany, Albany, N. Y., January 24, 1940, on "Advances in Management of Infectious Diseases."

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On January 16, 1940, Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, addressed the Academy of Medicine of Cincinnati on "Use of Liver and Iron in the Treatment of Anemia."

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Among the guest speakers at the fourth annual meeting of the Rhode Island Public Health Association, held in Providence January 23, 1940, with tuberculosis control as the topic of discussion was Dr. Herbert R. Edwards, F.A.C.P., New York, N. Y. Dr. Edwards is Director of the Tuberculosis Bureau of the New York City Department of Health.

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Dr. John H. Musser, F.A.C.P., Professor of Medicine, Tulane University of Louisiana School of Medicine, New Orleans, La., delivered a public lecture, sponsored by the Chicago Medical Society and the Chicago Heart Association, on "The Growing Importance of Coronary Disease," in Chicago, February 7, 1940.

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Among the officers appointed by the Society of Medical History of Chicago, January 31, were the following: President—Dr. Ernest E. Irons, F.A.C.P.; Secretary-Treasurer—Dr. George H. Coleman, F.A.C.P.; Councilors—Dr. James B. Herrick, F.A.C.P., and Dr. David J. Davis, F.A.C.P.

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Among those who addressed a recent meeting of the Jefferson County Medical Society of Louisville, Ky., were the following:

Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill., "Some Important Complications of Tuberculosis;"

Dr. Bayard T. Horton, F.A.C.P., Rochester, Minn., "Use of Histamine and Histaminase in Clinical Medicine."

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Dr. James B. Herrick, F.A.C.P., Chicago, Ill., addressed the Cleveland Medical Library Association at its annual meeting, January 19, on "Jean-Baptiste Bouillaud and His Contributions to Heart Disease."

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Dr. George E. Pfahler, F.A.C.P., Philadelphia, Pa., Professor of Radiology at the University of Pennsylvania Graduate School of Medicine, was honored at a dinner, January 25, 1940, sponsored by the Philadelphia Roentgen Ray Society. Among the speakers at this dinner was Dr. Joseph McFarland, F.A.C.P., Emeritus Professor of Pathology at the University of Pennsylvania School of Medicine.

## MINUTES OF THE BOARD OF REGENTS

Philadelphia, Pa., December 17, 1939

The regular autumn meeting of the Board of Regents of the American College of Physicians was called to order at 10:20 a.m., December 17, 1939, by the President, Dr. O. H. Perry Pepper, with Mr. E. R. Loveland acting as secretary, and with the following present:

O. H. Perry Pepper, *President*  
 James D. Bruce, *President-Elect*  
 J. Morrison Hutcheson, *Third Vice-President*  
 William D. Stroud, *Treasurer*  
 George Morris Piersol, *Secretary-General*

David P. Barr  
 Ernest B. Bradley  
 Sydney R. Miller  
 Walter W. Palmer  
 Robert A. Cooke  
 Ernest E. Irons  
 D. Sclater Lewis

Hugh J. Morgan  
 James E. Paullin  
 Francis G. Blake  
 Reginald Fitz  
 Charles T. Stone  
 Maurice C. Pincoffs  
 Charles H. Cocke

Specially invited guests to this meeting included Dr. William Gerry Morgan, Historian; Dr. James Alex. Miller, Chairman of the Finance Committee and the Committee on Survey and Future Policy; and Dr. Jonathan C. Meakins, a member of the Committee on Fellowships and Awards, the Committee on Survey and Future Policy and also of the American Board of Internal Medicine.

The Secretary, Mr. E. R. Loveland, read abstracted Minutes of the preceding meeting of the Board of Regents, April 29, 1939, and also the resolutions adopted at the meetings of the Board of Regents at New Orleans in March, 1939. The abstracted Minutes were approved as read.

The Secretary read communications as follows, each acted upon individually, as indicated:

- (1) Letters from Dr. Samuel A. Shelburne and Dr. M. D. Levy concerning the inclusion in the Directory of the College of additional biographical data, especially internships and residencies for each member.

On motion by Dr. Paullin, seconded by Dr. Pincoffs, and regularly carried, it was

RESOLVED, that action on the matter be deferred until the time for the preparation of the next edition of the Directory.

- (2) Letter from Dr. Walter A. Bastedo concerning representation on the U. S. Pharmacopoeial Convention.

On motion by Dr. Fitz, seconded by several and regularly carried, it was

RESOLVED, that a letter be written in the name of the College, asking that the American College of Physicians be listed as supporting the Convention, and that the President be authorized to appoint delegates, their expenses to be paid by the College.

Dr. Virgil Simpson, of Louisville, and Dr. Torald Sollmann, of Cleveland, were suggested as College delegates to the Convention.

- (3) Letter from Dr. Leo Kahn, Research Assistant to Senator Desmond, Albany, N. Y., concerning state examinations for specialists.

President Pepper pointed out that this would set up an additional licensing board, which possibly would be copied in other states, and that it would be at variance with the activities of the American Board of Internal Medicine.

Dr. Pincoffs stated that it was obviously in the hopes of forestalling such activity that the American Board was formed, and that the great disadvantage of having separate boards in every state is obvious.

On motion by Dr. Maurice C. Pincoffs, seconded by Dr. Hugh J. Morgan, and regularly carried, it was

RESOLVED, that the President of the College shall address a letter to Senator Desmond, Albany, N. Y., expressing the opinion that this College does not favor the formation of such boards, and pointing out the disadvantages thereof, and stating that our College has coöperated in the formation of the American Board of Internal Medicine, the purpose of which was to prevent separate and individual state licensing boards in the specialties.

The disapproval of the College was based primarily on lack of necessity, because the certifying boards already take care of this matter, and, therefore, it is not a matter of complete disagreement with the Senator from Albany.

- (4) A communication received by the President as Chairman of the Executive Committee of the Board of Regents, referring to the context of presidential addresses.

Certain of the expressions of opinion in some of the recent presidential addresses had not pleased the membership.

President Pepper pointed out that it would be difficult for the Board of Regents to dictate just what the President should say, but that he felt it proper that the Board should say to each President, and that each President should know that there has been some criticism concerning controversial matters.

Continuing, President Pepper said, "Your present executive finds himself denied almost every subject for a presidential address by one or another of these letters. Everyone agrees that the address should be inspiring, touch on important matters, should not be merely a report on the state of the College, although some think that is all it should be; that it should not touch on national or medical politics, should not touch on socialized medicine, should not touch too much on ethics, should not be a scientific contribution, should not be an attempt to be humorous—which all leaves the President in an almost impossible situation, although the President is fully in sympathy with some of the criticisms that have been made."

DR. PAULLIN: "Mr. President, I think you have stated the complaints that have been voiced from the groups and from individuals who have contacted me as being a member of the Board of Regents. In various sections of the part of the country from where I come they thought that since the Presidential Address is delivered at a time when new members are inducted into the College and since they assumed the address was delivered more or less to them as new members of the College, that they should be informed more of the activities of the College, of the purposes of the College, what the College had accomplished and what it intended to do, and not a learned or scholarly talk about possible advances in medicine. In other words, they wanted to know more of the College than they did of the things that are ordinarily discussed in state medical societies and county medical societies, and the American Medical Association. They have the idea that this College represents something more than a political organization attempting to fight for certain principles in the practice of medicine. They feel that the College is a separate and distinct organization from that and represents really the cream of medical thinking and medical practice and medical ideals."



DR. HUGH MORGAN: "I would like to go on record, if you are going to close the discussion, as stating that I think for a learned society such as ours, it is a pretty curious situation for the Regents at great length to consider what the President is going to talk about. Perhaps this is an indication that we should educate some of our members to the fact that it is all right for a person to have attitudes and points of view and to air them, and if we honor a man by making him President of this society, we can certainly tolerate his attitudes and personal opinions without being contaminated or without in any sense compromising the position of the society. I just feel that way about it and I don't think it makes a bit of difference what the President talks about, if we are what we say we are."

No special action was taken by the Board of Regents regarding directions for Presidential Addresses.

- (5) A letter from Dr. Cornelius O. Bailey, of Los Angeles, concerning an increase in the number of doctors and possible consolidation of the medical and dental professions.

Discussion of this communication was left for inclusion within the report of the Committee on Public Relations.

President Pepper pointed out that one of the matters of incompleting business from the Regents' meetings at New Orleans was action concerning the representation of this College on the Gorgas Memorial. He asked if any one was ready to speak on the matter. Since there was no discussion, the subject was laid on the table for further consideration at the Cleveland meeting, March 31, 1940.

The Secretary-General, Dr. George Morris Piersol, presented the following report, which was accepted as read:

"Since the last meeting of the Board of Regents, 31 Fellows and 10 Associates have died, as follows:

*Fellows:*

Allyn, Herman B., Philadelphia, Pa., November 6, 1939  
Barksdale, George Holt, Charleston, W. Va., October 8, 1939  
Bridges, Milton A., New York, N. Y., August 19, 1939  
Dube, Joseph E., Montreal, Que., November 25, 1939  
Edson, Philips Josiah, Pasadena, Calif., July 6, 1939  
Elliott, Charles A., Chicago, Ill., June 26, 1939  
Felts, Robert L., Durham, N. C., May 27, 1939  
Fligman, Louis H., Helena, Mont., July 18, 1939  
Franklin, George Charles Henry, Fort Leavenworth, Kan., April 23, 1939  
Friedlander, Alfred, Cincinnati, Ohio, May 28, 1939  
Hruby, Allan Joseph, Chicago, Ill., November 18, 1939  
Jackson, Byron Hubbard, Scranton, Pa., May 16, 1939  
Kamp, Joseph C., Casper, Wyo., May 13, 1939  
Keeney, Bayard G., Shelbyville, Ind., October 11, 1939  
Lineback, Paul Eugene, Emory University, Ga., February 28, 1939  
Macgregor, John A., London, Ont., September 20, 1939  
MacKenzie, Alexander John, Toronto, Ont., March 3, 1939  
Norbury, Frank Parsons, Jacksonville, Ill., March 14, 1939  
O'Malley, Mary, Buffalo, N. Y., January 30, 1939  
Pfozter, Roy G., Buffalo, N. Y., August 9, 1939  
Rice, James Francis, Watertown, N. Y., August 3, 1939  
Roberts, Carroll J., Buffalo, N. Y., April 6, 1939  
Rupert, Mary P. S., Bala-Cynwyd, Pa., July 21, 1939  
Rypins, Harold, Albany, N. Y., August 25, 1939

Smith, S. Calvin, Philadelphia, Pa., July 31, 1939  
 Soper, Willard Burr, New Haven, Conn., October 30, 1939  
 Stone, Charles W., Cleveland, Ohio, December 9, 1939  
 Stoner, Willard C., Cleveland, Ohio, November 16, 1939  
 Tappan, John W., El Paso, Tex., September 2, 1939  
 Trossbach, Herman, Bogota, N. J., October 1, 1939  
 Weigand, Frank J., Richmond Hill, N. Y., October 29, 1939

*Associates:*

Belknap, C. Herbert, Detroit, Mich., May 4, 1939  
 Cutler, Oran Idnre, Loma Linda, Calif., September 15, 1939  
 Murphy, John A., Philadelphia, Pa., June 13, 1939  
 O'Brien, Arthur Burke, Rochester, N. Y., July 6, 1939  
 Slaymaker, Samuel R., Chicago, Ill., May 3, 1939  
 Stein, Maurice Isaac, Harrisburg, Pa., August 15, 1939  
 Vrtiak, Emil George, Chicago, Ill., August 7, 1939  
 Walker, Thaddeus, Detroit, Mich., June 13, 1939  
 Walsh, John E., Washington, D. C., June 22, 1934  
 Yudelson, Albert B., Chicago, Ill., August 27, 1939

"Since the last meeting of the Board of Regents, the following Fellows have become LIFE MEMBERS of the College:

Edward L. Tuohy, Duluth, Minn.  
 Clarence L. Hyde, East Akron, Ohio  
 Clifford David Mercer, West Union, Iowa  
 Ernest John Aten, Ambridge, Pa."

The following report by the Committee on Public Relations was presented by the Chairman, Dr. James E. Paullin. The various matters recommended therein were acted upon separately and the report as a whole, upon motion by Dr. Paullin and seconded by Dr. Piersol, was approved and accepted as read:

"The following members of the Committee were present: Drs. Pepper, Cooke and Paullin.

"The substance of communications which have been referred to the Committee were sent to Drs. Walter L. Bierring, of Des Moines, and Noble Wiley Jones, of Portland, Ore., before the meeting of the Committee. Replies were received concerning all matters referred to them. Your Committee recommends to the Board of Regents the following:

"Acceptance of the resignations of Dr. Maud Loeber, New Orleans, La.; Dr. Ernst L. Schaible, Gary, Ind.; and Dr. George S. Lape, Binghamton, N. Y.

"We recommend that the following matters be filed as information:

- A communication from Mr. I. H. Rubenstein, of Chicago;
- A communication from Dr. William H. Walsh, Chicago;
- A communication from the Service Clubs Post No. 546 of the American Legion concerning matters relating to the increase of medical students is without the jurisdiction of the American College of Physicians.
- A communication from Dr. L. D. Boonschaft, of Los Angeles, concerning the regulation and standards for group practice of medicine is without the jurisdiction of the American College of Physicians.
- A communication from Dr. Edward W. McCloskey, of Philadelphia, concerning the furnishing of hospital records to osteopaths, etc., is without the jurisdiction of the American College of Physicians.

A communication from Dr. Ben R. Heninger, of New Orleans, concerning the use of an electrocardiograph on private patients in hospitals where ample facilities for such are available in the hospitals, and asking for an expression of opinion from the American College of Physicians. We wish to recommend that this is a matter for local solution.

The communication from Dr. J. N. Baker, Secretary of the Medical Association of the State of Alabama, requests that medical men be memorialized by Postmaster General of the United States having stamps struck in their honor. We thought this was a very worthy thing to be done."

President Pepper suggested that the Executive Secretary take care of all required communications, with the exception of the one to Dr. J. N. Baker concerning memorializing certain medical men by having postage stamps struck in their honor, the Chairman of the Committee to state that the American College of Physicians sympathizes with the move.

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, reported that his Committee on the previous day had reviewed the credentials of 150 candidates for Fellowship and 182 candidates for Associateship, and that an analysis of the recommendations was as follows:

A. Candidates for Fellowship:

(1) Recommended for election to Fellowship, 12-16-39	
(a) Advancement from Associateship .....	104
(b) Election directly to Fellowship .....	19
(2) Recommend election of advancement to Fellowship "as of March 31, 1940" ....	9
TOTAL, Fellowship elections recommended .....	132
(3) Recommended election to Associateship first .....	3
(4) Deferred for further qualifications .....	9
(5) Rejected .....	6
	<u>150</u>

B. Candidates for Associateship:

(1) Candidates recommended for election 12-16-39 .....	146
(2) Fellowship candidates recommended for election first to Associateship .....	3
TOTAL, Associateship elections recommended .....	149
(3) Deferred for further qualifications .....	20
(4) Rejected .....	14
(5) Withdrawn .....	2
	<u>185</u>

Chairman Miller distributed a list of all the names of candidates for review by the Board of Regents, and questions were answered concerning any and all candidates.

Upon motion by Dr. Sydney R. Miller, seconded by Dr. James E. Paullin, and regularly carried, it was

RESOLVED, the following list of 123 candidates shall be and herewith are elected to Fellowship as of this date, and the succeeding list of 9 candidates shall be and are herewith elected as of March 31, 1940 (Editor's Note—This list was published in the January, 1940, issue of this journal).

Upon motion by Dr. Sydney R. Miller, seconded by Dr. Robert A. Cooke, and regularly carried, it was

RESOLVED, the following list of 149 candidates for Associateship shall be and herewith are elected (Editor's Note—This list was published in the January, 1940, issue of this journal).

On recommendation of the Committee on Credentials, the following resolution made by Chairman Miller and seconded by Dr. Walter Palmer was unanimously adopted:

RESOLVED, that Dr. Howard M. Jamieson, Salisbury, Southern Rhodesia, shall be reinstated as a Fellow of this College.

On recommendation of the Committee on Credentials, moved by Chairman Miller, seconded by Dr. George Morris Piersol, and regularly carried, a resolution was adopted dropping seven Associates from the Roster because of failure to qualify for Fellowship within the five-year maximum term, as provided by the By-Laws. Chairman Miller reported that of 92 Associates elected at the December, 1934, meeting of the Board of Regents, 83 had qualified for advancement to Fellowship, 7 had made no effort to qualify and consequently were dropped, and 2 were deceased.

Chairman Miller then referred to a previous resolution of the Board of Regents, directing the Committee on Credentials and the Executive Secretary to formulate revisions of the booklet concerning membership requirements and other salient matters. He said that it was the intention of the Committee to improve the appearance of the booklet so that it shall be in keeping with the proper dignity and the contents should be changed in both form and substance. The substance of the booklet is now divided into four parts: an announcement which simply tells of the College and some of its activities, but not by any means all in its present form; a section which quotes the objects of the College from the Constitution; a section devoted to the discussion of the various types of memberships and the requirements for admission; a section given over to the matter of dues, fees and initiation.

Dr. Miller said the revision of this booklet involves not merely a rewriting to give the announcement a more comprehensive meaning, but it also involves the possibility of making amendments to the By-Laws to incorporate certain requirements which the Committee on Credentials feels should be taken up. Chief among such matters was the action the Regents might take in regard to the requirement that Associates shall be certified by the American Board of Internal Medicine, or the certifying board in an allied specialty, before coming up for Fellowship, on or after some given date yet to be determined. Dr. Miller stated that after consulting members of the Committee on Credentials, he felt that the introductory statement might be used almost in its entirety as it now appears in the College Directory. The use of this statement in appropriate form would obviate the necessity of a separate division devoted to the objects of the College.

At this point, Chairman Miller presented the following summarized statement of the problems which confront the Committee in connection with the revision of the booklet. (See next succeeding three pages.)

Chairman Miller pointed out that any amendments to the By-Laws must be published to the members one month prior to the annual meeting of the College before such amendments can be regularly adopted. Chairman Miller further stated that before the informative booklet is revised definite action should be taken with regard to two specific matters: (1) certification as a prerequisite for Fellowship; (2) the matter of the initiation fee, if such certification is made a prerequisite. The latter, Dr. Miller pointed out, if the College shall make certification a prerequisite for Fellowship, and since the certifying fee required by these boards is \$50.00, some consideration should be granted physicians toward a reduction of the initiation fee in the College. Dr. Miller suggested that the Fellowship initiation fee might be adjusted downward, as might also the fee for certification, so that the total fee shall not be greater than the present Fellowship initiation fee.

President Pepper requested Secretary Loveland to review from the Minutes the discussion in the Board of Regents at its last meeting in New Orleans concerning the

proposal of the Credentials Committee regarding certification, whereupon Mr. Loveland stated that Chairman Sydney R. Miller and Dr. George Morris Piersol, a member of the Credentials Committee, proposed that the Board of Regents should establish the regulation that after a certain date all candidates subsequently elected to Associateship should be required to be certified by the American Board of Internal Medicine, or the certifying board in an allied specialty, as a prerequisite for advancement to Fellowship, this requirement, however, not to affect other requirements already specified in the Constitution and By-Laws. It had been suggested, however, that this new requirement might be accepted in lieu of the presentation of case histories and autopsies.

Mr. Loveland stated that it was the opinion of the Credentials Committee that the present By-Laws would not need to be amended, since Article IV, Section a, of the Constitution provides, " Fellows . . . shall have been elected in accordance with the By-Laws and SUCH ADDITIONAL RULES AS THE BOARD OF REGENTS MAY FROM TIME TO TIME ADOPT."

After general discussion by President Pepper and members of the Board of Regents, on motion by Dr. Piersol, seconded by Dr. D. Sclater Lewis, and unanimously adopted, it was

RESOLVED, that on and after April 6, 1940, certification by the American Board of Internal Medicine, or by the appropriate board in their particular specialty, or country, shall be a prerequisite for Fellowship in the College. This rule shall not apply to Associates who shall have been elected prior to that date. (See a succeeding page for the final and approved wording of this regulation.)

Chairman Miller pointed out that the Committee will be confronted from time to time with proposals for election directly to Fellowship, and that the present By-Laws provide that such candidates shall have exceptional qualifications before the Committee may recommend their election. He stated that one of the criticisms of the present informative booklet is that there should be some statement or analysis of what those special qualifications must be. In the discussion that followed, it was apparent that this new regulation shall not necessarily prevent the election of very outstanding candidates directly to Fellowship.

It was suggested by Dr. Cooke that the "special qualifications" for election directly to Fellowship should be more specifically stated. Dr. Sydney R. Miller, Dr. George Morris Piersol and Dr. D. Sclater Lewis were appointed a committee to withdraw from the meeting and to more specifically draw up the exact wording of the resolution, to be submitted in connection with the report of the Committee on Survey and Future Policy, Dr. James Alex. Miller, Chairman.

On motion seconded and regularly carried, the report of the Committee on Credentials was accepted as a whole.

President Pepper called upon Dr. Hugh J. Morgan, Chairman, to present the report of the Committee on Postgraduate Education.

Dr. Morgan reported a meeting of his Committee on December 16, at which a tentative program, as follows, had been drawn up for the series of postgraduate courses to be given during the week or weeks immediately preceding the next Annual Session in Cleveland, April 1-5, 1940:

- No. 1. GENERAL MEDICINE—University of Michigan, Dr. Cyrus C. Sturgis, Director.
- No. 2. MEDICINE IN INDUSTRY—Henry Ford Hospital, Dr. Frank J. Sladen, Director.
- No. 3. HEMATOLOGY—Ohio State University, Dr. Charles A. Doan, Director.
- No. 4. METABOLIC DISEASES—Mayo Foundation, Dr. Russell Wilder, Director.

- No. 5. GASTROINTESTINAL DISEASES—Mayo Foundation, Dr. W. C. Alvarez, Director.
- No. 6. ALLERGY—Roosevelt Hospital, New York City, Dr. Robert A. Cooke, Director.
- No. 7. CARDIOVASCULAR DISEASES—State University of Iowa, Dr. Fred M. Smith, Director.

(Following the meeting of the Board of Regents, it was determined that the two courses at the Mayo Clinic could not be arranged, and they were withdrawn from the schedule.)

Dr. Morgan reported that the Committee had been slow this year in making definite plans relative to the postgraduate courses, because at the last annual meeting, the whole problem of the postgraduate courses, including the content and the conduct, had been considered by the Board of Governors, who had made a survey, and on whose report the Regents' Committee had waited.

Dr. Morgan also reported the request of a private clinic for the College to approve its postgraduate course in psychiatry. The College Committee on Postgraduate Education felt this would be a deviation from its previous duties and questioned the advisability of the College putting its stamp of approval on courses given under private auspices. Without special action, it was apparent that the Regents concurred in this opinion.

Dr. Morgan continued: "The final matter under consideration by the Committee concerns the rôle the College shall play in the field of postgraduate training in institutional practice. I think it would be useful to some members if we review briefly the things that led up to our present position relative to the decision we have made. In 1937, the Committee on Postgraduate Education was informed that the activities of the College in the field of postgraduate training at that time could be publicized at the Annual Meeting and in the 'Annals of Internal Medicine,' and the Board went on record that it wanted to do more than that in the field of postgraduate training, and that we should go into some sort of activity that would exert an influence on the quality of postgraduate training in medicine. At that time we considered an invitation from the American College of Surgeons to join with it in making a survey of hospitals as appropriate places for postgraduate courses in medicine. The Board of Regents and the Committee attended the College of Surgeons' meeting in New York City and received the invitation to go into the surveying of hospitals as places for postgraduate training in medicine. We felt loath to accept immediately, but very seriously considered their invitation. Directly after, the Council on Medical Education and Hospitals of the American Medical Association voiced an interest in this field, and Dr. Cutter, its Secretary, met with the Regents of this College in New Orleans and unofficially invited the College to consider working out some plan of using that Council as a means for making its contribution in this field. Then followed a meeting of the Board of Regents of the College with the Trustees of the American Medical Association in Chicago, the sense of which was that the College and the Council were interested in the same things, and there seemed to be no very good reason why some plan could not be worked out that, provided certain difficulties were ironed out, would enable the College to associate itself in some way with the Council, which was already in the field and doing an expensive piece of work. Representatives from the Board of Regents were then instructed to meet, with Dr. Capps and myself, with the Council on Medical Education and Hospitals at the St. Louis meeting of the American Medical Association, which we did. The Council was there informed of our invitation from the College of Surgeons, and also the Council was informed of those points that led to a feeling of hesitancy relative to our working out a plan with the Council on Medical Education and Hospitals. Two points came out that seemed important: first, the American Medical Association had put itself in a position of

rather decrying the importance of and, perhaps to some extent, of suppressing the expressions of specialty groups in medicine, specialty societies of which we are a very important one; and, second, the Council was brought into being by individual appointments each year of new members. This conference with the Council was very satisfactory, and out of it came an agreement that there certainly should be some plan by which the Council and the College could do a better job in this matter of postgraduate training, insofar as determining criteria for good positions in hospitals, residency training, fellowships, and actually surveying hospitals on the basis of these requirements and criteria.

"An individual from the Council, one from the Postgraduate Committee from the College and one from the American Board of Internal Medicine were appointed to consider some sort of plan whereby the College and the American Board could participate in a significant way with the work that the Council is doing. Your Committee has gone over this plan, which has been evolved, and a copy of which is placed in your hands. (See copy at end of Dr. Morgan's report.)

"The Committee believes that this plan offers a mechanism by which the College can play a very influential rôle in the activities of the Council on Medical Education and Hospitals of the American Medical Association. The Committee believes that one of the most important objections to the establishment of a relationship between the College and the Council was removed at the last meeting of the American Medical Association, in that the election of the Council members was removed from the field of political patronage and is now by election by the House of Delegates on nomination by the Board of Trustees of the American Medical Association. The Committee believes that the American Medical Association has reoriented itself to the governing bodies, certainly in one sense with regard to its attitude toward special societies. There is now a much healthier and more natural feeling with regard to those points. This plan will make it possible for the College, through its appointed representatives, and for the American Board to determine what the criteria are that shall be used in certifying positions as suitable for postgraduate training in medicine as would apply to the whole field in which we have been interested. The actual operation, the actual survey of the hospitals and institutions and study of the positions would be done by the machinery that has already been in existence some years in the Council. The standards would be furnished by this conference committee, and the results would be surveyed, approved or disapproved, by this committee before any action is taken, either by the Council, by the American Board, or by the College, to make the Council's findings official."

CHAIRMAN PEPPER: "This is an extremely lucid report, and brings the matter right up to us as to whether we approve."

DR. MORGAN: "If this proposal is adopted by the College, it must also be adopted by the American Board of Internal Medicine and by the Council of the American Medical Association, and when this is done, this conference committee will come into being."

On motion by Dr. Morgan, seconded by Dr. Stroud, and regularly carried, it was

RESOLVED, that the Board of Regents shall adopt the proposal for the establishment of a conference committee, as presented in the foregoing report, and that the President of the College shall appoint two members to this conference committee to represent the College.

#### "TENTATIVE PROPOSAL FOR ESTABLISHING A CONFERENCE COMMITTEE CONCERNED WITH GRADUATE TRAINING IN THE FIELD OF INTERNAL MEDICINE

"1. It is proposed that there be created a Conference Committee on Graduate Training in Medicine.

"2. The Conference Committee shall consist of two delegates from each of the following organizations: The American College of Physicians, the American Board of Internal Medicine and the Council on Medical Education and Hospitals of the A. M. A.

"3. The function of the Conference Committee on Graduate Training in Medicine shall be:

- "a) To submit observations and recommendations which may be useful in furthering the purposes of the constituent organizations.
- "b) To consider those elements which are regarded as essential in the appraisal of residencies, fellowships and systematic graduate courses for which the approval of the constituent organizations may be sought.

"4. Actual visitation of medical schools and hospitals for the purpose of securing information regarding standards and facilities for instruction in internal medicine shall in general be made by the staff of the Council on Medical Education and Hospitals; the Council will, however, welcome the assistance of qualified representatives of the College and the Board when such assistance is available. Information thus obtained shall be made regularly available to the Conference Committee.

"5. Residencies, fellowships or systematic courses in the field of internal medicine will be considered by the Conference Committee before independent action is taken by any one of the constituent organizations.

"While the foregoing memorandum covers the situation as far as the Committee understands the matter delegated to it, it is the feeling of the Committee that it may well be desirable to include members of other medical specialty boards in a conference pertaining to the problems of graduate training."

Dr. Paullin expressed his hearty approval of the proposal, and Dr. Irons, Chairman of the American Board of Internal Medicine, reported that the American Board had already approved of this proposal. He said the effect of this action by the College will have very farreaching results on the whole situation in graduate medical education.

Dr. Bruce commended the Committee and Dr. Morgan particularly on the successful termination of these conferences.

After the adoption of the resolution, President Pepper appointed to the conference committee Dr. Hugh J. Morgan and Dr. James D. Bruce, the latter appointment to be effective until Dr. Bruce's induction to the Presidency, when he may appoint a successor.

Dr. Hugh J. Morgan pointed out that he had first had the distinct impression that the College, in 1937, wanted to make a conspicuous contribution to the field of postgraduate training, and that the College anticipated the expenditure of funds to carry out such a program. The present plan now adopted, Dr. Morgan said, would not be a conspicuous contribution on the part of the College, but it should be very effective and would cost the College practically nothing.

Dr. Ernest E. Irons, Chairman of the American Board of Internal Medicine, reported that 2,133 physicians had been certified, of which 358 were certified by examination. The Board estimates that the probable number of examinees, 1939-40, will be between 225 and 235; 112 candidates appeared at the October 3, 1939, examination. The Board has labored to improve the quality and dignity of the examinations, and plans to obtain coöperation in examinations with the specialists in cardiology, gastro-enterology, etc. The annual budget of the Board is approximately \$5,000.00, and the Board has a balance of \$15,000.00. The Board further has approved unanimously the report of the joint committee proposed to establish a conference committee concerned with graduate training in the field of Internal Medicine.



Through questions put by Dr. Cocke and Dr. Paullin, Dr. Irons revealed that the number of failures had been much greater in the early operation of the Board than at present, but that the percentage still is about 23 per cent. For the last examination, the percentage of failures was estimated at about 30 per cent. This was due, Dr. Irons thought, to the fact that the Board has consistently increased the severity of the examination, and due to the fact that many candidates overestimated their degree of preparation. The Board feels that it must maintain its standards, and feels no apprehension about the number of candidates who will present themselves during the next year. The greatest mortality in the examinations naturally had been on the written part, because candidates must pass the written examination before coming up for the oral, and in that manner a larger proportion of the ill-qualified candidates are eliminated.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, told of the progress of former fellowship recipients; specifically, Drs. John Russell Smith, Harold Magnuson and Robert Williams.

The Committee recommended that the fellowship award made to Dr. Kenneth Evelyn, who could not take up the appointment July 1, 1939, be carried over, or re-awarded, for work in physics in medical problems at the Royal Victoria Hospital, Montreal, under the general direction of Dr. Jonathan C. Meakins.

On motion by Dr. Barr, seconded by Dr. Stroud, and unanimously carried, it was

RESOLVED, that the Research Fellowship in the amount of \$1,800.00 awarded to Dr. Kenneth Evelyn be re-awarded as of July 1, 1940.

On motion by Dr. Barr, in accordance with recommendations of the Committee on Awards, seconded by Dr. Bruce, and unanimously carried, it was

RESOLVED, that Research Fellowships in the amount of \$1,800.00 each be awarded to Dr. Richard Hugh Lyons and Dr. Lewis Dexter, beginning July 1, 1940.

Dr. Barr expressed the regret of the Committee that two additional fellowships were not available to two other promising candidates who had been under consideration.

There followed a general discussion concerning the great value of these fellowships awarded by the College.

On motion by Dr. Hugh J. Morgan, seconded by Dr. Paullin, and regularly carried, it was

RESOLVED, that the Committee on Fellowships and Awards shall select one of the candidates under consideration to whom an additional fellowship was not available as a substitute in case one of those appointed should not be able to accept, or in case an additional fellowship should become available.

Dr. Barr continued his report by stating that the Committee on Fellowships and Awards recommended the award of the John Phillips Memorial Medal for 1940 to Dr. René Dubos. The Committee had sixty representative scientists under consideration.

On motion by Dr. Barr, seconded by Dr. Palmer, and regularly carried, it was

RESOLVED, that the John Phillips Memorial Award for 1940 be made to Dr. René Dubos, of the Rockefeller Institute for Medical Research for fundamental investigations concerning the form, structure and function of microbial cells and concerning the lysis of bacteria; specifically for his studies of lysozyme, an enzyme which lyses many saprophytic organisms, and for the isolation of a soil bacillus elaborating a substance lethal to pneumococci and other gram positive members of the bacterial species. The award is made with the belief that aside from any or no immediate practical use the investigations have established a new principle of great importance in the study of cellular chemistry and of chemotherapeutic substances.

Dr. James Alex. Miller, Chairman of the Committee on Survey and Future Policy, presented the following report:

"A meeting of the Special Committee on Survey and Future Policy of the American College of Physicians was held at the College Headquarters, Philadelphia, Pa, on December 16, 1939, with the following present:

Dr. James Alex. Miller, *Chairman*

Dr. Jonathan C. Meakins

Dr. Sydney R. Miller

Dr. George Morris Piersol

Dr. Maurice C. Pincoffs

*Ex Officio*

Dr. O. H. Perry Pepper

"The Chairman of the Committee first outlined the purposes of the Committee as stated in the resolution of the Board of Regents authorizing its appointment. Then, as being also Chairman of the Finance Committee, the Chairman gave a brief review of the financial situation of the College, showing that on December 31, 1935, the cash and security assets of the College were approximately \$155,000.00, and that by December 31, 1936, after the present Headquarters were bought, altered and furnished, at an expense of approximately \$64,000.00, there remained assets of \$115,500.00. Each year since that time, there has been a surplus of income over expenses of somewhat over \$25,000.00 a year, and at the present time the total assets of the College, including the market value of investments and cash in hand, is slightly in excess of \$190,000.00. He also stated that the main sources of the surplus were from the initiation fees of new Fellows and the annual profit on the Commercial Exhibits at each Annual Session.

"*Certification and Qualification for Advancement from Associateship to Fellowship:* This question was fully discussed from various angles, and it was the general consensus of opinion that at the proper time, certification from the American Board of Internal Medicine should be a required qualification for advancement to Fellowship, and that this probably might become effective within a comparatively short time, possibly 1941 or 1942. This whole problem is being studied by the Committee on Credentials, of which Dr. Sydney R. Miller is Chairman, and he was requested to keep this Committee informed of the progress of their deliberations and of their proposed recommendations.

"*Initiation Fees and Annual Dues:* There was a thorough discussion of what needs there might be for excessive funds, such as are now being accumulated by the College. Also as to what might be considered the logical objective in the matter of invested endowment for the College. There was no definite action taken, but it appeared to be the general opinion that a gradual increase of capital up to \$500,000.00, which would assure a fixed income of approximately \$20,000.00 a year, would not be considered excessive. Inasmuch as the program for the increased expenditures for various possibilities has not yet been adopted, it was the general consensus of opinion that at the present time no changes, either in initiation fees or dues, would be wise, but it was brought out in discussion that if the requirement of certification was carried out, the fee for certification examinations, plus the initiation fee, might very well be excessive. In that connection, Dr. J. C. Meakins stated that a surplus was being accumulated in the hands of the American Board of Internal Medicine, and it was their hope that they might gradually diminish the fees for examination. After discussion, it appeared to be the general consensus of opinion of this Committee that a proper adjustment should be made at a suitable time between the fees required for the examination of the American Board of Internal Medicine and initiation fees of the

College, so that possibly the combined fee would not be greater than the present College initiation fee of \$80.00.

*"Commercial Exhibits:* Dr. George Morris Piersol, as Chairman of the Commercial Exhibits Committee, reported that the opinion of his Committee was that as present managed and supervised, the Commercial Exhibits had a very considerable educational value, that it was ethically of a high standard and that it would be entirely improper to abolish or curtail these exhibits, as has been at times suggested. The entire Committee agreed with Dr. Piersol that the Commercial exhibits should be continued as at present, with a continuation of the very close supervision and the maintenance of high standards.

*Scientific Exhibits:* A discussion ensued concerning the suggestion, which at times has been made for the College to institute a Scientific Exhibit in addition to the usual Commercial Exhibit. That there should be a scientific exhibit, it seemed to all of the Committee would be desirable. It was suggested that it might very well begin in a small way, confined to possibly one subject in Internal Medicine for the first year, and that the subject for the exhibit might very well also be made a subject for a symposium of a few papers on the general program. It was brought out that there are a great many scientific exhibits now being conducted, and that it would be very desirable to make a study of their experience. The Committee voted to recommend to the Board of Regents that the present President be authorized to appoint a special committee to investigate the subject of scientific exhibits and report to this Committee on Survey the results of such study.

*"Postgraduate Education:* A general discussion occurred concerning the future possibilities for the College in the line of Postgraduate Education. The experience of the present courses which are given before each Annual Session was discussed, and Dr. O. H. Perry Pepper suggested that the College might very well subsidize these courses in addition to the fees which are now being paid by the students.

Inasmuch as this whole question of Postgraduate Education is being studied by a special Committee of which Dr. Hugh J. Morgan is Chairman, it was suggested that this Committee take no action in this field, but request that it be kept informed of the progress of the studies of Dr. Morgan's committee, and of any recommendations which they may be prepared to make to the Board of Regents. The Committee suggests the possibility of having the Chairman of the Committee on Postgraduate Education made a member ex officio of the Committee on Survey and Future Policy.

*"Fellowships:* The possibility of using funds of the College for additional fellowships was also discussed, and it was voted to request from Dr. Barr that his Committee on Fellowships make recommendations to this Committee of any changes or additions that that Committee may consider desirable.

*"Educational Motion Pictures:* The possibility of the College taking the lead in making educational motion pictures in the field of Internal Medicine available to various teaching institutions was discussed. It was thought desirable that information be collected as to just what pictures of this sort were now available in various parts of the country. Consequently, Dr. M. C. Pincoffs, as Editor of the 'Annals of Internal Medicine,' was requested to put a news note in the 'Annals,' suggesting that the College was interested in having information concerning any such films that are available and asking any one who either possessed such films or had knowledge of where they might exist be requested to communicate such information to President Pepper, in the care of the College.

*"Bulletins Concerning Courses in Internal Medicine:* Dr. M. C. Pincoffs suggested that there was a lack of available information concerning postgraduate courses in Internal Medicine which are available in various parts of the country. It was suggested that the 'Annals' might act as a clearing house for such information by publishing each month a list of such courses with details concerning them. It was

voted by the Committee that Dr. Pincoffs explore these possibilities further and report to the Committee.

*"Development of State and Regional Meetings:* The Committee considered that the development of these local meetings is a very important and logical one for the College, and inasmuch as this program is one especially in the province of the Board of Governors, the Chairman of this Committee was requested to write to the Chairman of the Board of Governors, requesting that this Committee on Survey be informed of the progress that has been made to date and the plans which the Board of Governors have for the future in regard to such local meetings.

Adjournment.

JAMES ALEX. MILLER, *Chairman*

JONATHAN C. MEAKINS,

SYDNEY R. MILLER,

GEORGE MORRIS PIERSOL,

MAURICE C. PINCOFFS,

*Ex-Officio*

O. H. PERRY PEPPER

*Special Committee on Survey and Future Policy"*

President Pepper opened the report for general discussion from the floor.

On motion by Dr. Cocke, seconded by several, and regularly carried, it was

RESOLVED, that the President of the College shall appoint a special committee to investigate the subject of scientific exhibits, and to submit a report to the Committee on Survey the results obtained from such study.

President Pepper pointed out that this does not commit the College to a Scientific Exhibit, but merely is a preparation of data for later guidance. President Pepper appointed a Committee to consist of:

Dr. Francis G. Blake, *Chairman*

Dr. Robert A. Cooke

Dr. D. Sclater Lewis

On motion by Dr. Piersol, seconded by Dr. Paullin, and regularly carried, it was

RESOLVED, that the Chairman of the Committee on Postgraduate Education and the Chairman of the Board of Governors shall be added as members of the Committee on Survey and Future Policy.

On motion by Dr. Cocke, seconded by Dr. Palmer, and regularly carried, the report of the Committee on Survey and Future Policy was accepted as a whole.

At this point, the Chairman called upon Dr. Sydney R. Miller, Chairman of the Committee on Credentials, to present the formal motion regarding certification as a prerequisite for advancement to Fellowship. The following resolution was made by Dr. Miller, seconded by Dr. Paullin:

"RESOLVED, that after April 6, 1940, all candidates for Fellowship must present satisfactory evidence of certification by their national board for certification in their particular field, where such a board exists; this rule shall not apply to candidates from the Army, Navy and Public Health Services; it shall not apply to those who have been elected Associates prior to the above date; it may be waived in the cases of those proposed directly for Fellowship because of exceptional and outstanding qualifications."

In the discussion of the motion, Dr. Pincoffs expressed the opinion that this requirement would not seriously affect the number of candidates for Associateship, because it actually will not affect any newly elected Associates until those presented at the autumn, 1940, meeting of the Board of Regents, and these men would not be eligible for consideration for Fellowship for three years, and many would not qualify

until five years, or until 1945. During the interim, the American Board of Internal Medicine will have gained much more momentum, and the number of diplomates will be consequently increasing. Dr. Pincoffs expressed approval of a plan to adjust the Fellowship initiation fee at that time, so that there would be no increased financial burden exacted of this group of Associates because of having to be certified first by the American Board.

Dr. Piersol discussed several aspects of the motion, including:

- (1) The American Board of Internal Medicine is now certifying approximately 200 men a year, and that is about the number of Fellows ordinarily elected to the College, which would indicate that there will be an adequate number of certified men available for College membership.
- (2) The most important aspect of the proposal for certification affects the Credentials Committee; the Credentials Committee has experienced great difficulty in determining the professional and intellectual qualifications of candidates for Fellowship; the criteria set up in the By-Laws are totally inadequate; the case history system is unsatisfactory; from the earliest time, the Credentials Committee has looked forward to the time when some concrete method of determining the professional eligibility of Fellows could be established, even looking forward to the establishment of examinations by the College; when these certifying boards were established, there was no need to duplicate a complicated machinery; these boards, one of which was established under the College auspices, should be utilized for the technical examinations; the Credentials Committee is at a loss to know of any better method for determining the intellectual ability for Fellowship than this method of examination; if the proposal is adopted, all unnecessary, unreliable and variable means of determining men's ability will be eliminated, and there will be a yardstick which is clear-cut by which the Credentials Committee can definitely measure candidates' abilities.
- (3) The adoption of the proposal is not a complicated thing to achieve; the By-Laws and Constitution make it perfectly evident that the Board of Regents may, from time to time, at its discretion, change and set up whatever qualifications they deem wise for Fellowship; no revision of the By-Laws or of the Constitution is necessary.
- (4) When the present By-Laws were adopted, this particular provision was added for this specific purpose, so that there would be flexibility in extending the requirements for membership and the methods of applying such requirements.

Dr. Stone prophesied that the adoption of this regulation would not affect the College income from initiation fees more than one-third.

Dr. Fitz, speaking to the motion, said in part, "I am afraid that if we immediately adopt a resolution of this type, we may perhaps be doing something to destroy the present usefulness, ideals and philosophy of the College, because I do not think we have yet proved whether the specialty boards are of permanent value. I am impressed that the men now qualified do so for a variety of reasons. Some men may want to be certified for the sake of advertisement; some think that they can only get hospital positions by being certified, and some think that the scheme is new and fashionable, and are anxious to try it out. I don't think that a board operating so short a time is going to be permanently popular, or really going to be the type of thing that may even be desirable as time goes on. If you assume that more men are going to come up who want to go into general practice, and who do not want to be certified by a board, such as we have, how are you going to take care of them?"

DR. PINCOFFS: "We are to a certain extent committed to a very thorough trial at least, and a very whole-hearted trial, of the assistance of the American Board of

Internal Medicine, which we largely initiated. If this is a critical time in its development, it will be all the more critical if the body that started it is half-hearted in supporting it. This is the time when we should show our full support of the Board and see that it gets a very fair and full trial. Of course, its advantage is that it does attract a great many men for a variety of reasons, some very laudable and some very weak perhaps, but, nevertheless, it makes men work and study, and thereby raises the level of the practice of Internal Medicine."

DR. BRADLEY: "There is another consideration—as long as this proposal will not be written into the Constitution and By-Laws but be adopted merely as another rule of the Regents for the acceptance of Fellows, after trying it for five or six years, we may, without difficulty or delay, change the requirements and substitute others. This is not a regulation that must be made absolute for the future. The Committee on Credentials feels that we have long been postponing the adoption of this rule, but there has now come the time when something must be done, and I think if we are ever going to support the American Board of Internal Medicine we ought to do it now. I am in favor of this motion, and I think the proponents were right in leaving the way open to elect men directly to Fellowship who perhaps for adequate reasons may not be certified."

DR. COCKE: "For the sake of those who are not familiar with the discussions, this proposal does not mean, by any means, that certification is going to admit a man automatically to Fellowship. There will be other conditions and circumstances that the Credentials Committee will investigate before a man will be accepted. That should be specifically stated in the booklet concerning requirements."

President Pepper pointed out that this rule would not become effective until after the Credentials Committee had already passed upon candidates preceding their election to Associateship.

The motion was put and unanimously carried.

Next taken under advisement was the matter of whether or not there should be any amendment to the Constitution or to the By-Laws, because of this newly adopted regulation. Secretary Loveland was asked to read Article IV, paragraph 2, of the Constitution. It was the consensus of opinion that no amendments would be necessary, but that proper announcements should be made.

President Pepper suggested to the Chairman of the Committee on Credentials that that Committee should revise entirely its system of action and prepare a new publication of requirements later on, authorization already having been issued by the Board of Regents for the revision.

Dr. William Gerry Morgan, College Historian, was called upon for a report of progress on the preparation of the History of the College for its quarter of a century. Dr. Morgan stated that the history had been divided into two parts: first, a narrative of the founding and development of the College, and, second, the chronology of the College. The outstanding activities of the College would be presented in such a way that they would stand the test of criticism and of time, and to that end the Historian had invited men to write about certain specific activities of the College, and those men had been chosen because they were all Fellows of the College who had been either sponsors of or highly influential in developing those activities. Dr. George Morris Piersol, as Secretary-General, had contributed the preface for the volume; Dr. Maurice C. Pincoffs, as Editor, had contributed the chapter dealing with the publications of the College; Dr. Walter L. Bierring, as former Chairman of the American Board of Internal Medicine, had contributed the chapter on the part played by the College in the founding of that Board; Mr. E. R. Loveland, as Executive Secretary, had prepared the chapter both on the finances of the College and the development of the Constitution and By-Laws; Dr. Charles F. Martin had contributed a chapter

regarding the reorganization of the College between 1926 and 1929, and Dr. James Alex. Miller had contributed a chapter dealing specifically with the developments of the College from 1928 until 1940, with some prophesy with regard to the future. In the concluding part of the first section of the History, the Historian will have a chapter on the contributions of the Presidents, with a section also devoted to the men in less conspicuous positions who have contributed quite as much in their way to the progress and development of the College. The last section of the History will be called the chronology, and will contain a brief resume of the Minutes of the College which have been available from the beginning of the College in 1915 to the Cleveland meeting in 1940. Dr. Morgan said that the chronology will be of some value, particularly for reference. He estimated that the volume will contain between 300 and 350 pages. There will be approximately 50 illustrations, such as facsimiles of the original charter, various headquarters the College has occupied, its documents, such as the Fellowship Pledge, etc., etc.

Dr. Morgan described the many difficulties experienced in obtaining some of the data and in preparing a factual and interesting account. Dr. Morgan expressed the wish that the present Board of Regents would see fit to authorize the publication of the volume, and to make proper budget provision and to determine the method of distribution.

After general discussion, on motion by Dr. Piersol, seconded by several, it was

RESOLVED, that the Board of Regents authorize the publication of this History in book form and make an appropriation not to exceed \$3,000.00 to defray the expenses.

In general discussion that followed, Dr. Pincoffs pointed out that this book would appear in 1940 as an anniversary volume, and suggested that its publication need not be rushed for completion by the Cleveland Session in April, 1940.

There was general discussion as to the type of format, whether it should be distributed to all Fellows and Associates, and other relevant considerations. Secretary Loveland stated that Dr. Morgan had been modest in his presentation, and that Dr. Morgan had been put to some personal expense already in the preparation of the manuscript and for consulting fees with an expert bookmaker regarding a suggested format, type, size of illustrations and other matters. Mr. Loveland suggested that approximately 3,500 copies be published, and that a copy be given without charge to every active Fellow of the College and to new members as they qualified for Fellowship.

Dr. Cocke suggested that Dr. Morgan be reimbursed for all personal expenses he had borne, but Dr. Morgan refused reimbursement, saying that this work had been one of great interest to him, and that his contribution is only a small part of his devotion to the College over a great many years.

Dr. Fitz suggested that extra copies be printed, so that those who wanted to purchase them, either personally or for libraries, would be able to do so.

Mr. Loveland pointed out that the printer could be instructed to hold the type, so that a second printing could be made in case of need. The matters of format and arrangement were left in the hands of the Historian.

On motion by Dr. Blake, seconded by Dr. Bradley, and regularly carried, it was

RESOLVED, that the History shall be distributed to all Masters and Fellows of the College free of charge, regardless of whether the Fellows are paying dues or not.

It was pointed out that the volume will be placed on sale, and the price will be determined by the cost of publication.

Dr. Walter W. Palmer, Chairman of the Committee on the "Annals of Internal Medicine," stated that a meeting had been held to consider a problem brought up by the Editor, namely, the plan of accepting orders and distributing reprints to commer-

cial firms. The Committee, on the Editor's recommendation, suggested that authors shall continue to receive their reprints in any quantities at the published rates, and that they may pass on reprints to commercial firms, subject to the approval of the firms on the part of the Editor.

The Executive Secretary, Mr. Loveland, to clarify the situation, pointed out that the present recommendation would make it necessary that the College accept no orders for reprints from commercial houses, and that the College would in no way benefit from such orders. He explained that in the past, he, as the Business Manager of the ANNALS, had accepted an occasional order for reprints from commercial firms, the orders being approved by the authors, and the reprints furnished on order to the printers from the College. Inasmuch as the College placed the orders with the printers and thus controlled all such commercial orders and at the same time became guarantor for their payment, the commercial concerns were charged a slight mark-up over the prices of reprints to authors. The practice had been followed in accordance with the similar practice of many other scientific societies, and also from the standpoint of an equity on the part of the College to receive some return for its services and for its large investment in the publication of the ANNALS OF INTERNAL MEDICINE. The only particular exception to this practice that he had discovered was that of the American Medical Association, which furnishes reprints to commercial houses at the same rate it furnishes reprints to its authors. However, the American Medical Association is its own publisher and printer, and probably makes a profit not only on the reprints furnished commercial houses, but also on reprints furnished to authors. The American College of Physicians makes not one cent of profit on any reprints furnished to any author, and has as its object the furnishing of reprints to authors at the lowest possible cost. Mr. Loveland pointed out that the College has spent thousands of dollars in establishing its journal, and for the first several years of its publication, the College made up deficits amounting to additional thousands of dollars. Any surplus the College has enjoyed in recent years has not yet been adequate to make up the deficits sustained in the founding of the journal at its beginning. Mr. Loveland further emphasized the importance of controlling the acceptance of orders from commercial houses for reprints, and not to make it possible for the printers to accept such orders without the official sanction and knowledge of the College.

Dr. Pincoffs said that the College should continue its safeguards against the use of Annals articles as advertising matter by commercial firms. At present in those special instances in which there seems to be less objection to such use of reprints and when the author distinctly authorizes such use of his article, orders for reprints are to be handled in such a way that the author take written responsibility for any criticism that may arise in connection therewith. The College should not be further implicated by selling reprints to commercial firms.

Chairman Pepper stated that no action was called for, and the Committee's report would be received.

Dr. Pincoffs had no further report for the "Annals of Internal Medicine."

Dr. Edward L. Bortz, Chairman of the House Committee, could not be present because of illness, but his report was presented by Dr. William D. Stroud, a member of the Committee.

#### "REPORT OF THE HOUSE COMMITTEE TO THE BOARD OF REGENTS OF THE AMERICAN COLLEGE OF PHYSICIANS FOR DECEMBER 16, 1939"

"(1) The House Committee has had three meetings. The majority of the Committee's time has been taken up in the consideration of various suggestions for a suitable painting, portrait, inscription or emblem for the space above the fireplace in the Board Room.

"Several months ago the Committee decided to ask the Editor of the ANNALS to



publish a statement from the Committee requesting suggestions. But one reply was received by the Chairman of the Committee, that being from Dr. Jones of Louisiana, with the suggestion that a frame be made and hinged in place to hold a mirror. Later if a suitable picture were obtained, the mirror could be replaced.

"In a conference with the well-known architect, Mr. Edwin H. Fetterolf, the Committee requested Mr. Fetterolf to submit a sketch of the College Seal, which could be done in lead and suitably proportioned to fit the available space.

"While the Committee had no instructions regarding the amount of funds available for this work, the Committee suggested to Mr. Fetterolf that the charges for the same should not exceed \$500.00. It was further explained to the architect that the final decision concerning the nature of the Plaque and the amount to be expended rested entirely with the Board of Regents. That is where the matter stands at the present time.

"(2) Mr. and Mrs. M. R. Wiley, who live in the College home and receive a salary of \$100.00 a month, were engaged by Mr. Loveland as of June 1, 1939, to act as caretakers for the building and property at 4200 Pine Street. They occupy the rooms on the third floor. Their services have been satisfactory.

"(3) The building and property are in excellent condition. The cost of maintenance, including wages of caretakers, light, heat, gas and water, fire and liability insurance, taxes, compensation insurance, and general maintenance, for the year 1939 will be approximately \$3,470.00. The cost of rent and maintenance of the old offices at 36th & Walnut Streets, as far back as 1931, amounted to \$3,137.00, only a slight amount less for three small offices that were entirely inadequate and unsuited to the purpose. It might be appropriate to add to the present maintenance of the College Headquarters the allowance for depreciation of \$1,000.00. According to the directions of the Regents, the building is being depreciated \$1,000.00 per annum, until the valuation is reduced to the appraisal value of the land alone.

"During the past year, a guest room on the second floor has been appropriately furnished for the use of Officers, Regents and Committeemen who may come to Philadelphia on College business.

Respectfully submitted,

*The House Committee—*

T. GRIER MILLER

WILLIAM D. STROUD

EDWARD L. BORTZ, *Chairman*

In commenting upon the report, Dr. Stroud said that the Committee did not specifically recommend the acceptance of the report, leaving the matter to the discretion of the Board of Regents. The Committee felt, however, the report embodied the best solution of the treatment of the mantel space in the Board Room. The Committee had tried to find a portrait, or get some suggestions for a portrait, or a painting.

A motion made by Dr. Hugh J. Morgan, seconded by Dr. Cocke, providing for the acceptance of the report, was later withdrawn after discussion.

President Pepper said that he had been keenly interested in the Headquarters, and had hoped that an appropriate painting would some time come to our attention. He spoke unfavorably to the proposal to use a colored Seal of the College in the Board Room.

On motion by Dr. Cocke, seconded and regularly carried, it was

RESOLVED, that the House Committee shall continue its study further in an effort to find an appropriate painting for the College Headquarters' Board Room.

Dr. William D. Stroud, as Treasurer, presented the following report, which, on motion made, seconded and carried, was accepted:

"The present holdings of the College amount to \$90,403.75 in Bonds and \$84,255.00 in Stocks, at the present market price. Of this amount, \$70,948.75 in Bonds are in the Endowment Fund; \$19,455.00 in Bonds and \$84,255.00 in Stocks are in the General Fund. All the securities of the College cost \$177,252.56, whereas the present quotations amounted to \$174,658.75, showing a depreciation of \$2,593.81.

"As of 'March 19, 1939' (as reported at the New Orleans Session), our invested principal in the Endowment Fund was \$68,494.98 in Bonds; our General Fund, \$34,855.50 in Bonds and \$57,390.95 in Stocks, making a total value of \$160,751.43. The book value of that date was \$161,085.00, or a profit on investments of \$333.57."

Dr. James Alex. Miller, Chairman of the Committee on Finance, presented the following report, and filed a copy of the Minutes of the Finance Committee's meeting held December 16, in which specific purchase and sales of securities were authorized.

"The Finance Committee reports to the Board of Regents that the finances of the College are in extraordinarily sound condition, as already has been reported by the Treasurer.

"Quite a number of sales and purchases have been made during the year, all of which have been made on the advice of the Girard Trust Company, whose advisory service continues to give great satisfaction. It is to be noted that the present market value of all our securities is approximately \$174,000.00, while the purchase value is \$177,000.00, a decrease of only \$3,000.00, or 98.31 per cent in the value of the principal investment.

"The Finance Committee also recommends to the Board of Regents that securities of approximately \$30,000.00 market value be transferred from the General Fund to the Endowment Fund, thus bringing the market value of the Endowment Fund up to approximately \$100,000.00.

"It is also recommended that the selection of the particular securities to be so transferred be left with power to the Treasurer, with the advice of the Girard Trust Company.

"The Finance Committee has carefully considered the budget as presented by the Executive Secretary and, as presented, it has been approved with the following exceptions:

- (1) That the estimated income from investments be increased from \$5,700.00 to \$7,000.00, this being justified by the estimate of the Girard Trust Company;
- (2) The Finance Committee voted to recommend to the Board of Regents that the budget for the Executive Secretary's Office be increased by \$600.00, for increases in compensation to members of the office staff.
- (3) It was also recommended that an addition of \$200.00 be made to the budget for the President's Office for traveling expenses for the President.

Respectfully submitted,

JAMES ALEX. MILLER, *Chairman,*

CHARLES T. STONE,

WILLIAM D. STROUD,

*Committee on Finance"*

Dr. Miller presented financial reports showing income and expenses (estimated for December, 1939), budget comparisons with expenditures, cost analyses for the ANNALS OF INTERNAL MEDICINE, comparative cost analyses for the Annual Sessions and budgets estimating income and expenditures for 1940.

On motion by Dr. Hugh J. Morgan, seconded by Dr. Stroud, and regularly carried, it was

RESOLVED, that the Board of Regents approve of the transfer of approximately \$30,000.00, market value, of securities from the General Fund to the Endowment

Fund, the selection of the particular securities so transferred being left with power to the Treasurer, with the advice of the Girard Trust Company as Investment Counselor.

Dr. Miller, commenting on his report, said: "It is a disappointment to me as Chairman of the Finance Committee not to be able to recommend that the Committee approve a recommendation for additional fellowships. If that had come before us I am sure the Finance Committee would have approved the additional fellowships after hearing the report this morning of the Fellowship Committee. Perhaps it is not too late.

"I would just like to speak on one or two things. The first thing is to point out the extraordinary successful situation in regard to the "Annals." As you know, the subscriptions and advertising have been definitely increasing. We all know what an extraordinary successful journal it is going to be and now we are making a profit estimated in the neighborhood of \$6,000.00. There has been some comment about the very low cost of the College Headquarters. It is still hoped that in some way or other we may become tax exempt. Our taxes are about \$1,200.00. Since similar activities do not pay taxes, it would seem that a further effort might be made in that direction, and I think the Finance Committee would approve of suggesting to the Regents, at any rate, that further efforts be made to secure exemption from taxes."

On motion by Dr. Cocke, seconded by Dr. Hugh J. Morgan, and regularly carried, it was

RESOLVED, that \$600.00 additional, under item "2" of the Finance Committee's report, be appropriated and added to the 1940 budget.

On motion by Dr. Cocke, seconded by Dr. Hugh J. Morgan, and regularly carried it was

RESOLVED, that \$200.00 be added to the President's budget to be drawn upon for traveling expenses.

It was understood that this appropriation should apply also to the budget for 1939, as well as the budget for 1940.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, recommended that inasmuch as the Committee has two men of excellent caliber, who might be encouraged by the College to continue their work, two extra fellowships be awarded this year, beginning July 1, 1940, but in doing so, the College shall not make that a necessary precedent for subsequent years.

Dr. Barr pointed out that the College has been experimenting to some extent with these fellowships, and that it is possible as time goes along, the College may give more fellowships, or may change the character of these grants.

On motion by Dr. Barr, seconded by Dr. Bradley, and regularly carried, it was

RESOLVED, that the Board of Regents award two additional Research Fellowships, starting July 1, 1940, in the amount of \$1,800.00 each, to Dr. William Woods Beckman and Dr. Morris Tager.

Dr. Hugh J. Morgan, as Chairman of the Committee on Postgraduate Education, asked for the Regents' reaction to a plan by which the College would recognize the effort that men put into postgraduate teaching in the courses sponsored by the College by granting honoraria, supplementing the registration fees collected by the College. For instance, if the College has a group of ten, twenty or thirty men under the direction of some one person in a clinic or hospital for a week or two, would it not be a matter of good policy for the College to see that the director at least gets a sub-

stantial honorarium to the end that he will devote a substantial part of his time and thought to that work?

On inquiry to Mr. Loveland, it was revealed that the College expended \$566.15 during 1938, and \$462.27 during 1939 on the Postgraduate Courses, in addition to turning over all registration fees collected.

To be more concrete, Dr. Morgan suggested that the director of a two-weeks' course might be given an additional honorarium of \$250.00, and the directors of one-week courses might be given honoraria of \$150.00.

Dr. Cocke reported that he had heard criticisms that the heads of departments had not participated in the Postgraduate Courses, or given as liberally of their time as they should, and that Dr. Morgan's suggestion was one to encourage more active participation by such heads in these Courses sponsored by the College.

No action was taken making any appropriation or approving the plan of additional honoraria for directors of courses.

Dr. Meakins, as a guest at the Regents' meeting and a member of the American Board of Internal Medicine, was asked to express his opinions concerning the extension of fellowships. Dr. Meakins pointed out that the supply of assistant residencies and resident positions in teaching hospitals had become in many instances exhausted, and many young men who are aspiring to these positions must get their training in other ways. He suggested that good non-teaching hospitals might be stimulated to open assistant residencies and extend a resident system more completely than at present. He said there is a group of extremely good young men who could be helped by fellowships, but since there is a limit on the number that may be granted, the possibility, feasibility or advisability of creating loan funds at a nominal rate of interest to suitable candidates should be thoroughly investigated.

President Pepper pointed out that the College already has a Committee on Revolving Loan Funds, but that the Committee has not worked out an operating plan for adoption by the Regents.

On recommendation and motion by Dr. James Alex. Miller, seconded by Dr. Cocke, and regularly carried, it was

RESOLVED, that the Board of Regents adopt the 1940 budget, calling for an estimated income of \$105,600.00, and estimated expenditures of \$80,875.00.

President Pepper reported on arrangements for the Cleveland Session. He had attempted to meet criticisms of previous programs, to increase the number of papers by members of the College and reduce the number of guests, also to eliminate to a degree the repetitions of the same speakers that had appeared on our programs in previous years. By reducing the number of guest speakers the cost for traveling expenses likewise would be reduced. One session had been composed entirely of military papers, with the Surgeon Generals coöperating.

Dr. Pepper stated that he wishes to give a President's dinner to the Regents and selected guests, but would like to change the time of the dinner from Wednesday evening, preceding the Convocation, to another evening that would be free and not subject to the hurry entailed if the dinner were held preceding the Convocation. He reported that Dr. Charles F. Martin, the only Master of the College, had accepted the invitation to give the Convocation address. Dr. Martin is a survivor of a period when many interesting things happened in the reorganization of the College, and he will give a broad talk on the history of the College and its growth.

Dr. Pepper stated that he would like to depart from the usual formal Convocation procedure by personally introducing Dr. Martin in a more personal manner than by having his address announced formally by the Marshal.

Dr. Pepper further said that he had told the General Chairman, Dr. Howard T. Karsner, that it would be unnecessary for him to attend this meeting of the Regents,

and that by personal conversation, every possible point of importance had been covered in the preparations for the Cleveland Session.

Dr. Pepper described the program of local arrangements, appointment of committees by Dr. Karsner, the preparation of the clinic program by Dr. Joseph Hayman, Jr., and the preparation of the panel program by Dr. Harold Feil. Panels have been substituted in the place of the so-called round tables.

Dr. Pepper also spoke about local arrangements for the Smoker, entertainment of visiting women, the banquet, and other social matters. President Pepper had posted the program for the Cleveland Session in the Board Room for examination by all.

The Executive Secretary, Mr. Loveland, reported on business arrangements for the Session, including hotels, the auditorium, technical exhibit, Regents'-Governors' dinner, etc. He asked for directions from the Regents as to whether the dinner shall be a subscription dinner or one paid for by the College, the latter plan having been initiated last year.

President Pepper pointed out that the Regents'-Governors' dinner is conducted for the purpose of informal discussion and promotion of College matters. He expressed the hope that the dinner would be kept on a high plane, and would avoid, on one hand, formal speeches, but, on the other hand, would be open for formal discussion by any one who had ideas to present.

On motion by Dr. Paullin, seconded by Dr. Stroud, and regularly carried, it was

RESOLVED, that the expenses for the Regents'-Governors' Dinner be defrayed by the College.

President Pepper asked for suggestions from the Regents as to subjects that might properly and with benefit be discussed at the dinner, and suggested that the Chairman of the Board of Governors nominate some members from the Board of Governors to open discussion of important problems.

The Executive Secretary, Mr. Loveland, called the attention of the Board to possible meeting places for the College in 1941, pointing out that the city is selected at the last meeting of the Board of Regents during the Annual Session. He suggested that if any Regents have particular invitations in mind they be initiated without delay, so that all could receive proper consideration and investigation before time for voting arrives.

The following announcements were read: the next meetings of the Committee on Credentials are scheduled for February 25, 1940, at the College Headquarters, Philadelphia, and on March 31, 1940, at Cleveland; the next meeting of the Board of Regents will occur at 2:30 p.m., March 31, 1940, at Cleveland.

Adjournment.

Attest: EDWARD R. LOVELAND,  
*Executive Secretary*

## OBITUARIES

### DR. JOSIAH NEWHALL HALL

Dr. Josiah Newhall Hall, F.A.C.P., aged 80, of Denver, Colorado, died December 17, 1939, in Denver of pneumonia and myocarditis.

Josiah Newhall Hall, born North Chelsea (now Revere), Massachusetts, October 11, 1859, descended from John Hall, who came from England in 1652 and settled in Medford, Massachusetts. Father, Stephen Augustus Hall, a California "forty-niner," later farmer in Massachusetts. Mother, Evalina Amanda (Newhall) Hall, daughter of General Josiah Newhall of Lynnfield, Massachusetts. Bachelor of Science, Massachusetts Agricultural College, 1878, M.D., Harvard Medical School, 1882. House Physician Boston City Hospital, eighteen months.

Dr. Hall came to Denver, February 14, 1883, and on June 25, 1883, settled at Sterling, Colorado, then the only town (250 inhabitants) in a section of North East Colorado, larger than the State of Massachusetts. Three years later, Dr. Hubert Work, a later President of the A.M.A., Secretary of the Interior and Postmaster General, settled in Ft. Morgan, 45 miles away. These two men were the only physicians in that region. Dr. Hall was Mayor of Sterling in 1888-89. In 1892 he came to Denver. In 1891 he was President of the Colorado State Board of Medical Examiners and in 1903-04, President of the State Board of Health. In 1900 he was President of the Colorado State Medical Society. In 1916-17, he was President of the American Therapeutic Society. Dr. Hall wrote over one hundred and forty articles for the medical press. He also wrote the section on gunshot wounds, burns and scalds for Haines and Peterson's Legal Medicine and Toxicology. He wrote "Borderline Diseases," published by Appleton & Company in 1915. In 1893-97 he was Professor of Therapeutics at the University of Colorado. In 1897-1902 he was Professor of Medicine at the Gross Medical College and later at the Denver and Gross Medical College, which afterwards merged with the University of Colorado School of Medicine. In the last years of his life, he was Professor of Medicine Emeritus at the University of Colorado School of Medicine. In 1921-31 he served on the Judicial Council of the American Medical Association. Quite recently he published for private circulation among the members of the Colorado State Medical Society, his personal reminiscences of a busy, useful and most interesting professional life. The first of January, 1936, he was the earliest physician as to time of registration still active as a member of the State Medical Society.

During the war, he was Major in the Medical Corps and served 21 months, first as Chief of Medical Service at the Base Hospital, Camp Logan, Texas and then as Consultant in internal medicine to the Base Hospitals of the Southwest and Western cantonment base hospitals, and six other hospitals with a total of 30,000 beds. During this service he organized teaching clinics at various hospitals. During his professional career, Dr. Hall cared for several hundred of his colleagues affected with tuberculosis.

On April 12, 1885, Dr. Hall married Carrie G. Ayres, daughter of Felix G. Ayres, planter of Davis Mills, Mississippi. He had two sons, Sigourney D. Hall, automobile dealer at Fort Collins, and Oliver W. Hall, who died in Officers Training Camp, January 13, 1919.

Dr. Hall became a Fellow of the American College of Physicians in 1917, being one of the earliest members from the Rocky Mountain district. He was a member of the Board of Regents of the College and served as Governor for Colorado from 1925 until 1932.

Dr. Hall's interest in the history of the western country where he had made his home was given practical form in 1928 by the establishment of the Mrs. J. N. Hall Foundation for marking historic sites. Through the income from this \$5000 endowment, supplemented by additional funds from the same donor, the Colorado State Historical Society has been enabled to mark with bronze plaques more than forty sites of historical interest in Colorado.

Dr. Hall combined an amazingly alert mind with a retentive memory and an abundant energy even up to the last few months of his life. He was noted in the Rocky Mountain district for his brilliant diagnoses. He was greatly admired and revered by all his colleagues and "was widely beloved as a sincere, earnest, capable physician, as a leader in establishing the ethics and the true tradition of medical service."

JAMES J. WARING, M.D., F.A.C.P.,  
Governor for Colorado

### DR. DAVID MURRAY COWIE

David Murray Cowie, Professor of Pediatrics and Infectious Diseases and Chairman of the Department of Pediatrics at the University of Michigan Medical School, died on January 27, 1940, of coronary thrombosis.

Dr. Cowie was born in Moncton, New Brunswick, Canada, on November 19, 1872, and received his early education there. In 1889 he entered Battle Creek College where he studied for three years before enrolling in the University of Michigan Medical School from which he graduated in 1896. He was appointed assistant to the Professor of Theory and Practice of Medicine, Dr. George Dock, immediately after graduation, thus beginning a long and distinguished career in teaching, research and the practice of medicine. In 1906 he was made Instructor in Pediatrics and in 1907, Clinical Professor of Pediatrics and Internal Medicine. The following year was spent with Professor Krehl in Heidelberg. Upon his return to Michigan he resumed his duties in the Medical School and his private practice, and in 1920 was made Professor of Pediatrics and Infectious Diseases and head of the newly authorized Department. He held this position until his death.

His bibliography of over one hundred papers reveals a wide diversity of clinical and scientific interests. One finds the early years occupied in the analysis of various laboratory procedures and clinical technics of internal

medicine, with many contributions in gastro-enterology. This interest gradually merged into the more general fields of internal medicine and continued with the assumption of his responsibility for the teaching of pediatrics. During the two decades of his incumbency of the chair of pediatrics and infectious diseases, while he devoted himself to teaching, writing and research in that field, he always maintained an active interest in the broad aspects of internal medicine, enjoying in both fields a large, consulting practice.

Dr. Cowie served on the Council of the American Pediatric Society from 1913 to 1920 and was elected president of the Society in 1923. He was a Fellow of the American College of Physicians, the American Academy of Pediatrics, and the American Association for the Advancement of Science. He was president of the Michigan Allergy Society in 1937-38, chairman of the iodized salt committee of the Michigan State Medical Society since 1922, secretary of the University of Michigan Pediatric and Infectious Disease Society since 1933, and vice-president in 1920-21 of the American Society for the Advancement of Clinical Investigation. He was a member of the American Heart Association, International League against Epilepsy, Michigan Academy of Science, the Nova Scotia Historical Society and the Michigan Historical Society.

Dr. Cowie was a rare combination of the ideal family doctor, the wise professor, the able research worker, the skillful specialist, excellent teacher, efficient organizer and executive and, above all, an unselfish, loyal friend.

Thus is ended a distinguished career, marked by enthusiasm, energy, sacrifice, high intelligence and painstaking devotion to teaching, research and the care of the sick. He will be long and gratefully remembered by his colleagues, his students, particularly those whose good fortune it was to work intimately with him, and by a large and loyal group to whom he was always the beloved physician.

JAMES D. BRUCE, M.D., F.A.C.P.

### DR. FRANK HURD ROBINSON, JR.

The accidental death of Dr. Frank H. Robinson, Jr., of the Rockefeller Institute for Medical Research, New York City, an Associate of the American College of Physicians, in an automobile accident in Jamestown, N. Y., November 22, 1939, just at the time when he had begun to employ his splendidly trained talents in the practice of medicine, was not only a great loss to his community but to scientific medicine. Few physicians have brought to the practical application of medicine so many years of fruitful preparation.

As his teacher and advisor, through his medical studies and postgraduate work, I can affirm that he was the type of student that brings joy to a teacher's heart. Earnest, conscientious and ambitious to contribute to scientific medicine, he never failed to carry to a successful conclusion any problem to which he set himself.

His field work in the epidemiology of brucellosis, which was done in conjunction with the National Government, earned high praise, and his sub-



sequent work at the Rockefeller Hospital served only to confirm the reputation which his earlier work at Duke University had created.

This is not the place to review in detail Frank Robinson's scientific publications; these are recorded in medical literature for all time. One thinks, rather, of Frank Robinson the cheerful friend and happy companion. All who knew him called him "Robbie" and the diminutive was one of affection. He was very serious when at work, but loved to play, and a party was always a jolly one when Robbie was there. He had a sound mind in a sound body and rejoiced in using both in all forms of professional and social activity. His death has left a void in the hearts of his friends who will always remember him with a wistful sadness because of his all too early death.

FREDERIC M. HANES, M.D., F.A.C.P.,  
Durham, North Carolina

### DR. NORMAN IRVING BROADWATER

Dr. Norman Irving Broadwater (Associate) of Oakland, Md., died January 3, 1940, in the Memorial Hospital at Cumberland, Md., of cerebral hemorrhage.

Dr. Broadwater was born in 1882 and received his medical training at the University of Maryland School of Medicine and College of Physicians and Surgeons, graduating in 1909. He had been an Associate of the American College of Physicians since 1926, having originally been a member of the American Congress on Internal Medicine from 1924.

Dr. Broadwater through his ability as a careful clinician and his kindly interest in his patients occupied an important position in the field of internal medicine in his community. His death is a great loss to his many devoted patients and to his large circle of friends in the medical profession.

### DR. PETER CLINTON PUMYEA

Dr. Peter Clinton Pumyea was born in Hightstown, N. J., November 8, 1880 and died January 18, 1940.

Dr. Pumyea received his B.S. degree at Princeton University in 1901 and his degree of Doctor of Medicine at Columbia University College of Physicians and Surgeons in 1905. He served an internship at City Hospital in 1906 and started the practice of medicine in 1907 in New York City. He was formerly Director of the Medical Service and President of Medical Board at The Central Neurological Hospital; Attending Physician at Welfare Hospital; Associate, Cardiac Clinic at Roosevelt Hospital; in 1939 he became a member of the Welfare Hospital for chronic diseases as Visiting Physician in Medicine (open Division). He was a Member of the New York State Medical Society, the New York Academy of Medicine, The American Medical Association, and an Associate of the American College of Physicians since 1916.

CHARLES F. TENNEY, M.D., F.A.C.P.,  
Governor for Eastern New York

# ANNALS OF INTERNAL MEDICINE

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## WHAT IS AN INTERNIST? \*

By O. H. PERRY PEPPER, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

PRESIDENTS annually come and, fortunately for you, Presidents annually go. Each performs his duties as well as he can; each meets certain problems which he solves if he can, and each year at the Convocation the President addresses you on the state of the College or on some phase of our College or professional activity. As one reads the Presidential Addresses of past years, one is impressed by the learning and wisdom of my predecessors in this office. They have settled all sorts of tremendous problems—political, ethical, medical, sociological—the discussion of which required the utmost bravery. On the other hand, these brilliant gentlemen have demonstrated a marked degree of timidity in one direction. As one reads their addresses, one sees them getting closer and closer to a certain question, then suddenly turning away and avoiding it. This is quite amazing for this question is of some importance to our College and to each of us, for it concerns what we are and what we do.

Like these former Presidents, I have done my best to perform the duties of the office and have felt deeply as each of my predecessors must have felt, that his little service to the College is a very inadequate evidence of his appreciation of the honor which he has received from the College. Among these duties which each President must perform is the delivery of an address at the Convocation. For this he must select an appropriate and interesting topic. In seeking for such a subject I have sought help during the past months and the only suggestions received have all had to do with the very matter which former and wiser Presidents have avoided. Also the College has received a number of letters asking for some statement on this matter. And so for these reasons and to remove the stigma of cowardice from the Presidents of the College, I am tempted to discuss the question "What is an Internist?"

Now we are physicians and doctors and we know what these words mean. Together we are joined to form an American College of Physicians and

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\* Presidential Address, delivered at the Convocation of the American College of Physicians, Twenty-fourth Annual Session, Cleveland, April 3, 1940.

the meaning of these words is well understood. Perhaps you would think that this should be sufficient and that like the Presidents of past years we might continue to avoid the attempt to define an internist. But we all use this word and we should not do so unless we can justify ourselves. It is not enough for us to say that we know what an internist is, so why bother to define it. Words without a clear meaning should not be used. Perhaps onomatopoeic words need no definition for they repeat the desired sound as, for example, thunder and borborygmus. But even slang has a reason for every word and phrase even though we often fail to know its origin.

And even if we do not admit that we should try to understand the words we use, we should realize how much pleasure we lose if we do not appreciate the origin, derivation and implication of them. Take, for example, the word "sincere." How much meaning it gains when we remember that its origin dates back to the days when if a marble statue was so perfect that there was no crack needing to be filled with wax, it was called *sine cera*, in other words, without wax. So, today, when we sign ourselves "yours sincerely," we mean without any wax, which brings us very close to the modern slang use of the words "soft soap" or "the old oil." I am sure that a clear understanding of all that internist means will likewise lead to a more enjoyable use of the word.

It is science and its followers who should especially be prepared to define accurately its every term, to justify its every word and to be certain that every word has a clear meaning and only one. So it seems that an attempt should be made to define this term "internist," which we all use, even if in making the attempt I prove myself foolhardy. Perhaps the old saying might be paraphrased to read, the novice slashes in where master surgeons fear to cut, and perhaps in the final analysis I shall fail and shall have to claim that like squaring the circle, it just cannot be done. But even if I, personally, did not feel the urge to try this task, it is clearly the duty of the American College of Physicians to define an internist, for Article III of our Constitution refers to our membership as composed of "qualified internists of high standing." Furthermore, our College has decided that all those elected to Associateship from this time on, in order to be eligible for advancement to Fellowship will have to present certification by the American Board of Internal Medicine, which body also has used the term "internist" in its printed folder of information.

So you see the question is an important one to us and faces us on all sides. We cannot laugh it off as we so often do the importunate questions of our patients. We must undertake to find an answer, however inadequate it may be. Certainly it will be some help in disproving the widespread belief of the layman that an internist is the same as an intern. If any of you think that this statement is incredible, let me assure you that it is a fact and further that a recent edition of an authoritative dictionary flatly states that the word internist is a synonym for intern. No doubt it is true that both of these words refer to those doctors who practice within walls but these walls differ;

in one instance being those of the hospital; in the other, those of the body. I am sorry to say we must protest against being confused with interns, however much we envy them their youth and opportunities.

Other dictionaries and the rest of the laity if they have heard the word at all, define an internist as one who practices internal medicine. This may perhaps be as good a definition as is possible but it is certainly inadequate in several directions. In the first place, it merely substitutes one difficulty for another for we lack a satisfactory definition of internal medicine; and secondly, it does not go half far enough.

An attempt to formulate a definition of internal medicine was the text of the Presidential Address by Dr. Reynold Webb Wilcox in 1916 at the first scientific session of the American Congress on Internal Medicine of which our College was a member. He tried to delimit internal medicine by listing twelve categories of disease which together formed its domain, and went on to state that the name internist is undoubtedly the proper one and that an internist is not only a specialist but an expert. We will return to this thought later. Dr. Wilcox went on to say that the American College of Physicians had created an aristocracy among internists, a point of view reiterated by George Vincent in his 1929 address to the College when he called us an elite.

Internist apparently was an acceptable designation twenty-five years ago but is still misunderstood and not in general use throughout our country today. It is amusing to read in the Transactions of that Congress that one of those who discussed the President's Address suggested that a journal be published, to be named "The Internist," which should have as one of its major purposes the equalization of the fees of the surgeon and the internist. Surely this was and is a desirable goal; had it been successful it would have made the word very much more familiar and the internists very much wealthier. Unfortunately the venture was never launched and so neither of these beneficial results was ever reached.

Apparently the term "internist" grew out of the need for a name for the doctor who practices internal medicine and certainly this term "internal medicine" was in use long before the designation "internist" was coined. One can trace the phrase internal medicine far back into the nineteenth century and it would appear to have been used in Germany and France before being adopted in England or in this country. But it was employed with various shades of meaning and it is difficult to find a satisfactory definition of this division of medicine.

One of William Osler's most famous addresses was entitled "Internal Medicine as a Vocation" and all the wisdom of that great essay is as true today as it was in 1897. It should be familiar to all of us and it can be found in that volume of his collected essays which takes its name "Aequanimitas" from the finest of them all. Osler was a very great man but even he does not really define Internal Medicine in that address and expresses the wish, to quote his words "there were another term to designate the wide

field of medical practise which remains after the separation of surgery, midwifery, and gynecology. Not itself a specialty (though it embraces at least half a dozen), its cultivators cannot be called specialists, but bear without reproach the good old name physician, in contradistinction to general practitioners, surgeons, obstetricians and gynecologists."

Nor does Osler trace the history of the origin and growth of internal medicine as distinct from the practice of medicine. This also is difficult to do for its beginnings are hidden in the story of the progress of all medicine. From one point of view it has been done by Prof. Knud Faber of Copenhagen, in 1923, in one of the most fascinating books about internal medicine ever written. It is entitled "Nosography in Modern Internal Medicine," and in it he traces the development of internal medicine as reflected in the constant effort to find a workable classification of disease. Faber divides the history of internal medicine into six parts—first Sydenham and the Nosologists; next the Paris School with its emphasis on anatomic diagnosis. Then followed in order the German school of physiologic medicine, the bacteriologic clinic with Pasteur as its chief exemplar and finally the periods of functional diagnosis and of constitutional pathology. Throughout the book most of the famous figures are referred to as clinicians though many of them would not be so considered today. It is not until Faber refers to Soupault and his observations in 1901 on the symptoms of chronic gastric ulcer that the term internist appears.

In my own opinion the first physician who displayed the point of view which in some ways is the hall mark of the internist, was Sydenham when three centuries ago he turned away from the old confusions of theory without fact to actual observations of fact. This was Sydenham's real contribution and far more important than his oft quoted advice to young students of medicine "Read Don Quixote." That no doubt shows his appreciation of the fact that the physician must know human nature but it might have been better if Sydenham himself had given more attention to the new discoveries of Harvey and of Malpighi which in fact he neglected, although his contemporary Sir Thomas Browne considered Harvey's discovery to be preferred over that of Columbus.

Following him Boerhaave, Bichat, Auenbrugger, Laënnec, Louis, Koch, Graves, Stokes, Corrigan, Bright and Addison, to name only a few, each in his turn laid stones in the growing foundation of Internal Medicine. These men were internists in a measure and were followed by many others on down the list to recent times when only chronologic proximity lessens due recognition. Other famous men whose discoveries made it possible for such a thing as internal medicine to evolve were in no sense internists—Pasteur, Virchow, Claude Bernard. Even Thomas Hodgkin who was a physician was not really an internist.

Long before internal medicine had appeared surgery had become a separate specialized branch of medicine, obviously because of the fact that anatomy, so essential for surgery, was the first of what we term today the basic

sciences, to supply a body of information beyond the ability of assimilation of the general practitioner. Also the need of special manual ability hastened the flowering of surgery. Internal Medicine had to wait until the accumulation of knowledge of physical diagnosis, clinical medicine and of therapy had added to it the basic facts of physiology, bacteriology, biochemistry and pharmacology to form a body of knowledge requiring the full attention of anyone who would be familiar with it all.

This is the mechanism which acts to split branches and specialties off the main trunk. It is not a decision but an evolution. When the mass of information and of technic grows so large that it can no longer be included in the general knowledge of the practitioner then it is allotted to that certain group who willingly learn this at the cost of all else. It is as inevitable as evolution and cannot fail; but, on the other hand, hasty attempts to anticipate the process on the basis of inadequate aggregates of specialized knowledge are equally certain of failure. Internal Medicine came about properly and in due course, and as a further step in the same direction came into being this group of individuals who are, in the first place, physicians, next practitioners of internal medicine and finally internists.

So now we come back to our starting point—the name internist. It is not such a new word as some might think nor is it so clearly understood or widely adopted as others would believe. In various parts of this country it is scarcely known at all and such terms as diagnostician, medical consultant or even clinician are applied to that individual who elsewhere would answer to the name internist. None of these other terms is as satisfactory for this purpose; diagnostician excludes therapy which is an inherent function of the internist; nor should the internist be thought of as one who sees patients only in consultation. In no way can an internist better exhibit his skill than in the personal physician to patient relationship. There is even less excuse for the use of the word "clinician" in this connection. Internist is the best term even though it has not established itself as yet.

It is hard to trace its very beginnings. Undoubtedly it was used in France and Germany before coming to this country. I cannot find it in the Index Catalogue of the Library of the Surgeon General nor in any of Osler's many essays, nor as I have already said, do the dictionaries help us. Apparently it stemmed from internal medicine and if it had originated in England or here might just as well have been internalist as internist. In fact, some dictionaries define an internist as one treating only the diseases of the internal organs. But it came from the French "interniste" instead.

This is the background of our problem and it is easy to see two reasons why a satisfactory definition has not, and perhaps never will, be put into words. The first of these arises from the fact that the word we are trying to define is derived from the term "internal medicine," which in turn is undefinable and which in the very nature of things is changing its meaning from decade to decade. Its borders are not fixed; it is not a mere matter of internal and external medicine. What at one epoch may belong to the

domain of internal medicine may shortly be excluded and on the other hand, the advance of science may bring new or return old, divisions of knowledge to its fold. Clearly if internal medicine cannot be better defined than the exponent of this field, the internist, can only be described in terms of the field itself.

In the second place, our difficulty depends upon the inherent nature of a definition. All that a definition can do is to define and to delimit; it is a flat statement of the basic meaning of a word as determined by derivation and usage. A definition is static and dead. Internal medicine and the internist are neither static nor dead and never will be. Nor will all the full meaning of these words ever be included in any definition. But let us state a definition for better or worse, and then let us consider what any such definition will inevitably fail to express. It must be worded somewhat in this fashion:

An internist is a physician fitted by a sound and applicable knowledge of the basic sciences, a continuing training in clinical medicine, a familiarity with fields outside his own, and an intellectual rather than a manual or technical approach, to study, diagnose and treat the diseases of the field of internal medicine to which he strictly limits himself and to integrate with the knowledge of his own field that of the allied specialties.

This may be far from satisfactory but it comes as near to telling the truth and nothing but the truth as I have been able to make it. But does it tell the whole truth? By no means! For to us the word "internist" has a far wider meaning than that which can be encompassed by any definition. Through use the word has gained and grown until today it is a living thing with secondary accessory implications—heard like the overtones of a musical chord. The student of harmonics can define the note C or a given chord and can also recognize but cannot accurately define the many overtones which only the trained ear can hear. But the enumeration of the overtones of the word "internist" is a still more difficult matter.

Let me describe what I hear in this word "internist":

An internist is, of necessity, a physician of exceptional training for his is the field of greatest width. He must have served his apprenticeship years acquiring information, then slowly transformed that essential but relatively base metal into precious knowledge and still unsatisfied, devoted his maturer efforts to the transmutation of knowledge into priceless wisdom.

An internist is one who with sufficient foresight has been willing to pass through what Sir Andrew Clark termed the ten years of dry bread, and the ten years of bread and butter, in order to reach the final twenty years of cakes and ale. He is one who has followed Osler's admonition "Let him not lose the substance of ultimate success in grasping at the shadow of present opportunity."

Being an internist is a state of mind. It implies a breadth of interest which inherently excludes narrow specialism. It demands a vital interest in

medicine of the past, of the present, and as far as possible of the future. The true internist is an "ingenious man" in the old sense of that word, when it was properly used to indicate an active intellectual inquiring mind. The highest praise that Samuel Pepys could give was—"He was an ingenious man." Our internist is of such a nature and his interest in science extends beyond medicine proper, without loss of sympathy with the suffering individual.

Interest in many fields of human thought must be a characteristic of every internist, for humanity and all its doings fascinate him. Culture in its true sense of simple appreciation of the fine products of human skill, art and endeavor belongs to such a nature. Similarly a high moral code and strict ethics are essential ingredients in this picture which we are sketching. Intellectual courage and high standards of duty to his work, to his patients and to his community are inherent to his personality.

These are a few of the overtones and implications which I hear in this word "internist." Each of us has known some such individuals, each of us has some exemplar upon whom we would model ourselves. He may have been some outstanding historical figure such as those we have named or he may be some humbler or more recent figure not yet known to fame but if he be an internist with all that this term implies, he is without doubt the highest type of the physician which evolution has produced.

We like to think that our College is composed of individuals who possess in great measure all these qualities which the term "Internist" implies. We pride ourselves that our Fellows are seeking to achieve such high goals.

You, newly elected members, are admitted to the College because in you are recognized the potentialities, the material and the spark necessary to make you achieve the stature of the ideal internist. See to it that you gain inspiration from being a part of this great College and that in turn you add to its glory by your own efforts and success in making of yourself an internist. If this conception of what it means to be an internist is true, then your task is no easy one but the challenge of difficulty is a strong stimulant and the laurels of success are to be gained in many directions besides those of the material rewards of this world.

I hold very strongly that the internist should not be too narrowly specialized within the field of Internal Medicine. On the contrary, he should be highly specialized in Internal Medicine and if, for any reason, he becomes particularly interested in one or another sub-division of this field, he must, to retain the title "Internist" in its full sense, continue his familiarity with the whole domain of Internal Medicine. If I read the signs of the times correctly, the need today is for more true internists rather than for more internists who have become specialized in limited sub-branches. The field is open for the well-trained internist and I hope that more and more of the members of this College will qualify themselves for this high task.

Nothing that you are being asked to be or to do is new or peculiar to the internist, but perhaps as internists you should exhibit these qualities in



the highest degree. The principles involved almost antedate medical history, you will hear them tonight in the Oath of Hippocrates and you will find them in that other still older Oath of the Hindu Physician. "Devote yourself to the healing of the sick even if your life be lost by your work." "Do the sick no harm." "Always seek to grow in knowledge."

And now let me draw two conclusions from what has been said: first, that if our delineation of an internist is a true one, then our College must reword its Constitution for how can it refer to "highly qualified internists" when there can be no such creature as an unqualified internist. If he be not in all things excellent, then let him not be termed an internist.

Secondly, that if this brief characterization of an internist be the truth, it is obvious at once that never will it be included in a definition. We see at once why no President has ever offered a satisfactory definition and why no one ever will. The subject is an endless one and it might become the repeated topic of many annual convocational addresses without fear of repetition in the same fashion as the ever old but ever new, annual lectures on "The Care of the Patient" at Harvard.

Personally, I find some comfort in the classical story of the brilliant Greek poet Simonides who when Hieron challenged him to define the nature and attributes of God asked for a day's time to prepare his answer, and the next day begged for two days more, and on each occasion doubled the period that he required for thought. When at last Hieron demanded an explanation, Simonides replied that the longer he pondered the matter, the more obscure it became. And that is where the matter of a definition of an internist rests for all of me.

And now in closing let me leave this thought with you. It is of the very essence of life that it should be impossible to define certain things. An internist is such an undefinable entity and this is as it should be. To be defined he must be standardized, and if he be standardized then even if he be all that we have added unto him yet shall he fail—for with standardization dominant, no one, internist or otherwise, can be what he needs to be to be above all else—himself—an individual—a man.

# FUNCTIONAL AORTIC INSUFFICIENCY \*

By CURTIS F. GARVIN, M.D., *Cleveland, Ohio*

ORGANIC aortic insufficiency has been recognized since Cowper<sup>1</sup> first described this condition anatomically in 1706. The physiological changes attracted attention in 1715 when Vieussens<sup>2</sup> noted the collapsing pulse. Further important diagnostic signs were recorded by Hope<sup>3</sup> in 1831.

The observations of Corrigan<sup>4</sup> in 1832 concerning the mode of origin, meaning and character of the auscultatory and palpatory phenomena of aortic insufficiency stimulated interest in the condition and thereafter the literature increased steadily. Relative aortic insufficiency came to be recognized, and in 1896 Barié,<sup>5</sup> in an article entitled "True and False Aortic Insufficiency," made a comprehensive review of the contributions to that date.

Subsequently numerous observers have reaffirmed the association of aortic dilatation and relative aortic insufficiency with chronic hypertension or granular kidneys. These reports have tended to indicate that the occurrence of the condition is rare.

The present communication indicates that relative aortic insufficiency is more frequent and more important than is generally supposed. Two hundred consecutive autopsied cases of hypertensive heart disease were studied and 14 instances of relative aortic insufficiency were discovered, an incidence of 7 per cent. All of these cases were seen on the medical divisions of Cleveland City Hospital, and although in some instances there was a difference of opinion as to the significance of the aortic diastolic murmur there was no question as to its existence. The importance of the lesion is apparent when one considers that in several instances it led to frank errors in diagnosis. The salient details of these cases are noted in the following case reports.

## CASE REPORTS

*Case 1.* A. F., a 65-year-old white male, had had symptoms of myocardial insufficiency for one year. On examination three observers heard a prolonged low-pitched loud diastolic murmur to the right and left of the sternum in the second and third interspaces. The cardiac conduction mechanism was normal. The blood pressure was 210 millimeters of mercury systolic and 110 diastolic. The patient died on the second hospital day. The clinical diagnosis was syphilitic aortic insufficiency and myocardial insufficiency.

The autopsy showed evidence of chronic myocardial insufficiency. The heart weighed 700 grams. All the heart valves were normal. The aortic valve ring measured 7.5 cm., normal for a male of this age being 8.03 cm., according to Roessle.<sup>6</sup> The pericardium was not adherent, the coronary arteries showed moderate to marked sclerosis, and there was generalized arterial and arteriolar sclerosis. The final diag-

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nosis was generalized arterial and arteriolar sclerosis, coronary artery sclerosis, myocardial fibrosis, cardiac hypertrophy and dilatation, and myocardial insufficiency.

*Case 2.* W. C., a 63-year-old colored male, had had symptoms of myocardial insufficiency for two years. Examination showed a soft diastolic murmur at the aortic area. The murmur was inconstant. The cardiac conduction mechanism was normal. The blood pressure averaged 160 millimeters of mercury systolic and 110 diastolic. The Wassermann test was negative. The patient died on the one hundred twenty-eighth hospital day. The clinical diagnosis was hypertensive heart disease, the diastolic murmur being considered insignificant.

The autopsy showed a dilated heart weighing 450 grams, coronary sclerosis, and generalized arterial and arteriolar sclerosis. All the heart valves were normal. The aortic valve ring measured 8.5 cm., average normal for this age and sex being 8.03 cm. The final diagnosis was as in Case 1.

*Case 3.* E. P., a 35-year-old colored male, had had symptoms of cardiac failure for six months. He had had a chancre 13 years previously. Seven observers agreed as to the presence of a to-and-fro murmur heard best at the aortic area and to the left of the sternum but also at the apex. The cardiac conduction mechanism was normal and there was a gallop rhythm. The blood pressure was 150 millimeters of mercury systolic and 110 diastolic. The Wassermann test was four plus. The patient died on the one hundred forty-sixth hospital day. Because the murmur was not constant, most of the clinical observers believed this to be hypertensive heart disease with a functional aortic insufficiency, although the possibility of luetic aortic insufficiency was considered.

The autopsy showed typical findings of hypertensive heart disease with failure. The heart was dilated and weighed 650 grams. All the valves were completely normal. The aortic valve ring measured 9 cm., the normal value for a patient of this age and sex being 6.46 cm.

*Case 4.* A. B., a 53-year-old colored female, had had symptoms of cardiac failure for 13 months. On examination five observers heard a loud diastolic and a softer systolic murmur over the upper chest. The cardiac conduction mechanism was normal. The blood pressure was 180 millimeters of mercury systolic and 60 diastolic. The Wassermann test was negative. The patient died on the twenty-fourth hospital day. The clinical diagnosis was syphilitic aortic insufficiency and heart failure.

At postmortem examination the heart was dilated and weighed 575 grams. There was generalized arterial and arteriolar sclerosis. The valves were normal. The aortic valve ring measured 9 cm., the normal for a patient of this age and sex being 7.09 cm. The final diagnosis was hypertensive heart disease with cardiac failure.

*Case 5.* J. E., a 59 year old colored male, had had symptoms of myocardial insufficiency for three years. According to four observers there was a loud to-and-fro murmur at the aortic area. The cardiac rhythm was auricular fibrillation. The blood pressure could not be determined exactly but was considered to be 150 millimeters of mercury systolic and 50 diastolic. The Wassermann test was negative. The patient died on the day of admission. The clinical diagnosis was syphilitic aortic insufficiency with heart failure.

At postmortem examination the heart was dilated and weighed 650 grams. The valves were normal. The aortic valve ring measured 8 cm., the normal value for this sex and age being 7.77 cm. There was moderately severe coronary sclerosis. The final diagnosis was as in Case 1.

*Case 6.* E. W., a 41-year-old colored female, had had symptoms of myocardial insufficiency for one year. A diastolic aortic murmur of medium intensity was heard by six different examiners. The cardiac conduction mechanism was normal and the blood pressure was 220 millimeters of mercury systolic and 98 diastolic. The Wassermann test was negative. The clinical diagnosis was syphilitic aortic insufficiency and heart failure.

At postmortem examination the heart was dilated and weighed 525 grams. The valves were normal and the aortic valve ring measured 6.5 cm., normal being 6.8 cm. The final diagnosis was as in Case 1.

*Case 7.* W. K., a 50-year-old colored man, had had symptoms of myocardial insufficiency for two years. Four observers agreed to the presence of a to-and-fro murmur, with the diastolic element loudest at the aortic area. The blood pressure on admission was 170 millimeters of mercury systolic and 90 diastolic, and this subsequently fell to 110 systolic and 80 diastolic. Coincident with this the diastolic murmur disappeared. The Wassermann test was four plus. The patient died on the one hundred first hospital day. On admission the clinical diagnosis was syphilitic aortic insufficiency, but when the murmur disappeared the diagnosis was altered to cardiac hypertrophy and failure with incidental luetic aortitis.

The autopsy showed the heart to weigh 475 grams and to be dilated. The valves were normal and the aortic valve ring measured 9 cm., normal being 6.95 cm. There was a luetic aortitis without dilatation of the aorta, narrowing of the coronary ostia or extension to the aortic valve. The cause of the cardiac hypertrophy and cardiac failure was obscure. The final diagnosis was cardiac hypertrophy and failure.

*Case 8.* D. Y., a 44-year-old colored male, had had symptoms of cardiac insufficiency for one year. Five examiners heard a diastolic murmur at all areas, loudest at the aortic. The cardiac conduction mechanism was normal. The blood pressure was 210 millimeters of mercury systolic and 120 diastolic. The Wassermann test was four plus. The patient died on the twenty-fifth hospital day. The clinical diagnosis was hypertensive heart disease with heart failure and relative aortic insufficiency due to cardiac dilatation.

At postmortem examination the heart was dilated and weighed 700 grams. The valves were normal. The aortic valve ring measured 8 cm., normal being 6.95 cm. There was an uncomplicated syphilitic aortitis. Generalized arteriolar sclerosis was present. The final diagnosis was hypertensive heart disease with cardiac failure, and syphilitic aortitis.

*Case 9.* L. J., a 45-year-old colored female, had had symptoms of myocardial insufficiency for six months. Four observers heard a to-and-fro murmur at the aortic area and to the left of the sternum. The cardiac conduction mechanism was normal. The blood pressure was 130 millimeters of mercury systolic and 100 diastolic. The Wassermann test was four plus. The patient died on the seventy-eighth hospital day. The clinical diagnosis was syphilitic aortic insufficiency with cardiac failure.

The autopsy showed a dilated heart weighing 375 grams. The valves were normal and the aortic valve ring measured 8 cm., normal being 6.8 cm. There was no syphilis of either the aorta or the aortic valve. The final diagnosis was as in Case 3.

*Case 10.* J. D., a 58-year-old colored male, had had symptoms of myocardial insufficiency for six months. Four examiners heard a to-and-fro aortic murmur. The cardiac conduction mechanism was normal and the blood pressure was 160 systolic and 100 diastolic. The Wassermann test was negative. The patient died on the thirty-fourth hospital day. The clinical diagnosis was syphilitic aortic insufficiency and heart failure.

The autopsy showed a dilated heart weighing 460 grams. The valves were normal and the aortic valve ring measured 8.5 cm., the normal being 7.77 cm. There was no syphilitic aortitis. The final diagnosis was as in Case 3.

*Case 11.* G. C., a 62-year-old colored male, had had symptoms of myocardial insufficiency for one month. There was a history of lues with inadequate treatment. Four examiners heard a short diastolic murmur to the left of the sternum. The cardiac conduction mechanism was normal. The blood pressure was 210 millimeters of mercury systolic and 138 diastolic. The Wassermann test was negative. The clinical diagnosis was hypertensive heart disease. The aortic insufficiency was variously considered to be due to either sclerosis or syphilis.

At postmortem examination the heart was dilated and weighed 550 grams. The valves were normal. The aortic valve ring measured 8 cm., normal being 8.03 cm. There was marked arterial and arteriolar sclerosis. There was no syphilitic aortitis. The final diagnosis was as in Case 3.

*Case 12.* W. D., a 78-year-old colored male, had had symptoms of myocardial insufficiency for eight months. Four examiners heard a loud diastolic aortic murmur. The blood pressure was 190 millimeters of mercury systolic and 70 diastolic and the cardiac conduction mechanism was normal. The Wassermann test was negative. The aortic insufficiency was considered to be organic, probably due to sclerosis.

The autopsy showed a dilated heart weighing 625 grams. The heart valves were normal and the aortic valve ring measured 9 cm., normal being 8.2 cm. The final diagnosis was as in Case 1.

*Case 13.* T. K., a 38-year-old white female, had a two year history of myocardial insufficiency. Six observers heard a to-and-fro aortic murmur from time to time. The blood pressure was 250 millimeters of mercury systolic and 160 diastolic. The cardiac conduction mechanism was normal. The Wassermann test was negative. The patient died on the forty-eighth hospital day. The clinical diagnosis was hypertensive heart disease. The murmur was variously ascribed to rheumatic valvulitis or ring dilatation.

The autopsy showed a dilated heart weighing 450 grams. The valves were normal. The aortic valve ring measured 6.5 cm., normal being 5.73 cm. There was severe vascular disease and nephrosclerosis. The final diagnosis was as in Case 3.

*Case 14.* E. B., a 68-year-old colored female, had had symptoms of myocardial insufficiency for 18 months. Three examiners heard a moderately loud aortic diastolic murmur which subsequently disappeared. The blood pressure was 210 millimeters of mercury systolic and 100 diastolic. The cardiac rhythm was auricular fibrillation. The Wassermann test was negative. The clinical diagnosis was hypertensive heart disease.

At postmortem examination the heart was dilated and weighed 510 grams. The valves were normal. The aortic valve ring measured 10 cm., normal for this age and sex being 7.65 cm. The final diagnosis was as in Case 3.

## COMMENT

It will be noted that in the majority of these cases the murmur was loud and easily heard so that there need be no doubt concerning its presence. Furthermore, in most instances four or more observers agreed to its existence. The wide pulse pressure (averaging 85 millimeters of mercury) is confirmatory evidence of an aortic leak. This is in contrast to the fact that the pulse pressure in the 186 cases of hypertensive heart disease without aortic insufficiency averaged 65 mm. of mercury.

The clinical interpretation of these murmurs is interesting. In Cases 1, 4, 5, 6, 9 and 10 the aortic insufficiency so predominated the picture that an outright diagnosis of syphilitic heart disease was made. In Cases 3, 11 and 12 it could not be decided whether the murmur was due to syphilitic aortic valvulitis or sclerosis of the valves. In Case 13 the murmur was considered to be characteristic of aortic insufficiency and was variously thought to be due to rheumatic valvulitis or dilatation. The working impression in Cases 2 and 7 was syphilitic aortic insufficiency, but in these two cases the murmur disappeared so that the final diagnosis was hypertensive heart dis-

ease. In Case 14 an initial impression of arteriosclerotic aortic insufficiency was abandoned when the murmur proved to be transient. The correct diagnosis of functional aortic insufficiency was made in Case 8.

Although the series is small, the high incidence of colored patients is striking, i.e., 12 out of 14 (86 per cent). This is in contrast to the fact that in the 186 cases of hypertensive heart disease without aortic insufficiency there were 66 colored patients (35 per cent). The percentage of males and females was practically the same in the cases with and without murmurs.

The autopsies in these cases showed a rather constant picture: evidence of severe myocardial insufficiency, marked cardiac dilatation and normal heart valves with special emphasis on the fact that the aortic valve showed no anatomical abnormalities. The aortic valve ring in these 14 cases averaged 8.25 cm. in circumference, whereas the average of the normal values for these cases is 7.3 cm. None of the cases showed pericardial adhesions. Cases 7 and 8 had syphilitic aortitis but there was no dilatation of the aorta and no aortic valvulitis. There was rather uniform anatomical evidence of hypertension in the way of generalized arteriolar sclerosis and arteriolar nephrosclerosis. The pathological findings clearly indicated that the aortic insufficiency noted in life was functional and not due to anatomical changes in the valve leaflets.

In a personal communication to the author Dr. R. W. Scott has described the case of a 17-year-old boy who was the victim of malignant hypertension. This patient, even when his circulation was compensated, had a characteristic murmur of aortic insufficiency. By administering amyl nitrite, the blood pressure could be temporarily lowered, the diastolic aortic murmur would disappear, and the second sound would become tambouric and clear. Whether this will aid in the differential diagnosis of functional and organic aortic murmurs in the face of the severe dilatation of heart failure remains to be seen.

#### SUMMARY

A survey of 200 consecutive autopsied cases of hypertensive heart disease discloses 14 cases in which a diastolic murmur was heard at the base of the heart. This finding led to varying degrees of difficulty in clinical interpretation. In four instances a frank error in etiological diagnosis was made. At autopsy the heart in these cases was dilated but showed perfectly normal valves. In fact, the pathological findings permitted no other conclusion than that the aortic insufficiency noted in life was functional and not due to anatomical changes in the valve leaflets.

It is thought that functional aortic insufficiency occurring in cases of hypertensive heart disease is more common and more important than is generally recognized.

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## PRESENT STATUS OF THE PULPLESS TOOTH \*

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THE status of the pulpless tooth has undergone a definite change in the last few years. Reëducation of the physician, as well as the dentist, on this point is both necessary and timely. It will, therefore, be the object of this paper to define the pulpless tooth and interpret the facts concerning it in the light of recent studies.

At the outset it must be made clear that periapical infection can, and sometimes does, cause infection elsewhere in the body. The frequency with which such foci of infection exist and cause systemic disease is open to question, however, and has without doubt been greatly overemphasized in the past. The author is in agreement with the following statement of Billings,<sup>1</sup> who did so much to place the concept of focal infection before the medical profession: "Focal infection as a cause of disease has come to stay. But, like every other principle in medicine, it has its limitations."

Experimental evidence, as well as clinical observation, of the relationship of dental foci of infection to systemic disease is not lacking. Rosenow and Meisser<sup>2</sup> have experimentally produced renal calculi in dogs by removing the pulps of teeth and sealing streptococci in the root canals. Following a somewhat similar technic Jones and Newsom<sup>3</sup> succeeded in producing myocardial changes in dogs, e.g., vegetative or verrucose lesions in the region of the mitral or aortic valves, parenchymatous degeneration, and round cell infiltration. The dogs became fatigued more easily than normal controls, and presented symptoms somewhat similar to those generally associated with heart disease in the human. Haden<sup>4</sup> produced peptic ulcers in dogs by injecting a culture prepared from bacteria recovered from the roots of infected teeth of patients suffering from peptic ulcers.

In addition to the few experimental studies cited here, numerous clinical case reports would seem to attest to the validity of the focal infection theory. Bierring<sup>5</sup> has recently reviewed the more important literature dealing with focal infection, and an excellent summary of the status of oral focal infection is given by MacNevin and Vaughn.<sup>6</sup> It is not the purpose of this paper to question the validity of the focal infection concept. It is only desired to point out that, on the basis of recent studies, focal infection from pulpless teeth occurs less often than was previously thought. It must be emphasized also that although a focus of infection may be present, e.g., around the root apices of certain pulpless teeth, it does not follow that focal infection is also present. The latter term implies systemic dissemination from the focus.

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## MISCONCEPTIONS CONCERNING THE PULPLESS TOOTH

It is desired first to clear up two popular misconceptions regarding the pulpless tooth. Since 1910 it has been the general opinion of many physicians and dentists alike, (1) that a pulpless tooth is a "dead" tooth, and (2) that Hunter<sup>7</sup> aimed his shaft of criticism against the pulpless tooth.

A pulpless tooth is not a dead tooth. It still has a definite and vital relationship with the surrounding tissue. Because of the peculiar anatomic and structural make-up of the dental tissues, the erroneous concept of a "dead" tooth gained currency. Actually, the life of the tooth depends upon its attachment apparatus, i.e., periodontal membrane and adnexa. In the words of Marshall<sup>8</sup>: "The life of the tooth is dependent upon the integrity of the periodontal membrane and not upon the integrity of the pulp." As a matter of fact, many embryologists believe that the function of the pulp ceases when the tooth is completely calcified, shortly after eruption. If a pulpless tooth were a dead tooth, it should be exfoliated, since the body seldom tolerates dead tissue. That a pulpless tooth is not dead may be evidenced by the pain experienced upon its removal without an anesthetic.

In his history-making address in Montreal in 1910, Hunter<sup>7</sup> did not refer specifically to the pulpless tooth as a source of oral sepsis when he condemned the kind of dentistry then prevalent. How the pulpless tooth came to be maligned instead of the accumulation of filth around ill-fitting crowns and bridge-work, against which Hunter inveighed, will probably never be known. The entire matter is summed up in a much overlooked but important editorial<sup>9</sup> in the *Journal of the American Dental Association*. The editor referred to Hunter's criticism as follows: "The 'oral sepsis' of which he complains, and not without reason—had nothing whatever to do with the thing that, during the decade that followed his address, caused the greatest concern among the profession, i.e., focal infection from apical ends of pulpless teeth. This is the thing that claimed our major consideration, and in connection therewith the name of Hunter has repeatedly been quoted. As a matter of fact, Hunter never referred in the remotest way to the evils of pulpless teeth as such. He was concerned with the sepsis that came from accumulations around crowns, bridges, and artificial dentures, calling them 'gold traps of sepsis.' . . . Mayhap if this distinguished scientist had given his whole-hearted attention to this important question, the mental aberration and almost universal prejudice against the pulpless tooth that has developed might have thereby to a certain degree been avoided." That this misconception could have been perpetuated for so many years is indicative of the hysterical era which followed Hunter's criticism. Had his words been taken literally, the orgy of extraction, that continued for more than two decades, might have been averted.

Studies bearing on the pulpless tooth as a possible focus of infection may be divided into: I, clinical; II, roentgenologic; III, histologic; IV, bacteriologic. Only the more important findings in each group will be discussed here.

## I. CLINICAL STUDIES

1. It is a well known fact that a large number of people having pulpless teeth show no apparent systemic involvement. It is also significant, perhaps, that no definitely conclusive proof has yet been advanced that, in any case, a tooth or teeth were the direct cause of the systemic disturbance, excepting a priori proof. The extraction of a tooth followed by amelioration of symptoms does not necessarily prove that the tooth was the cause of the disease. This is only an assumption which may or may not be true.

2. During the World War draft, data were collected of more than two and one-half million men between the ages of 18 and 30 years. An evaluation of the data, according to Appleton,<sup>10</sup> shows that "chronic infection about the head is not . . . the sole determining factor in the contemporaneous occurrence of such conditions as gastric ulcer, appendicitis, endocarditis, arthritis, osteitis deformans, myositis, and muscular rheumatism."

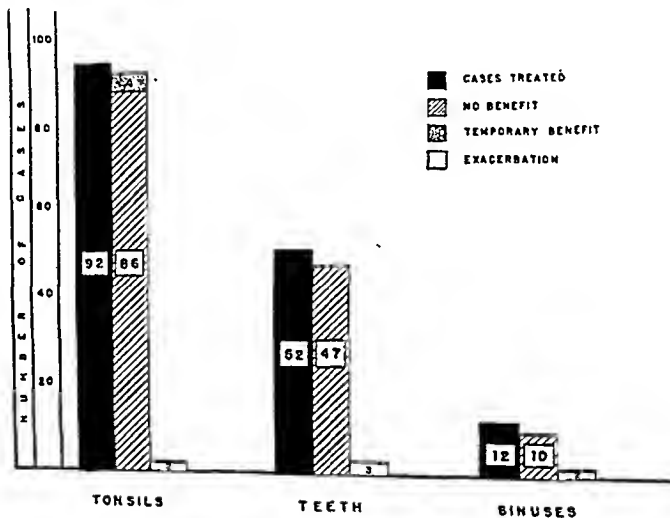


FIG. 1. The results of treatment of tonsils, teeth and sinuses in a group of 200 patients with rheumatoid arthritis (Cecil and Angevine: *Ann. Int. Med.*, 1938, xii, 577).

3. Frankel<sup>11</sup> studied the incidence of systemic disturbances in a large group of people with and without so-called "heavy dentistry." By this term he meant the presence of crowns, bridges, pulpless teeth and any other dental evidence which might suggest the presence of a focus of infection. He concluded that the incidence of systemic disturbances in the "heavy dentistry" group was not materially higher than in the other group.

4. Cecil and Angevine<sup>12</sup> recently analyzed the results of the elimination of foci of infection in 200 cases of rheumatoid arthritis. They came to the conclusion that no benefit accrued to 47 out of 52 patients for whom dental foci of infection were removed (figure 1).

## II. ROENTGENOLOGIC STUDIES

1. Full mouth roentgen-ray pictures of more than 1500 patients were studied by Ziskin<sup>13</sup> to determine whether a direct correlation existed between positive roentgen-ray findings of pulpless teeth and systemic disturbances. The subjects were patients in the wards of a city hospital, from the out-patient department of the same hospital, and ambulants who applied only for dental treatment and who were well otherwise. Ward and outpatient subjects were examined by the medical staff and complete medical histories were available. The following is a synopsis of the study: (a) 48 per cent of the subjects studied were sick, 52 per cent were well; (b) 71 per cent of the "sick" group and 75 per cent of the "well" group had pulpless teeth; (c) of those with pulpless teeth, 46 per cent were sick and 54 per cent were well, whereas of those without pulpless teeth, 50 per cent were sick and 50 per cent were well. From these findings it is obvious that a relationship between pulpless teeth and systemic disease in the groups studied is certainly not striking.

2. Arnett and Ennis<sup>14</sup> made complete routine medical and dental examinations of 883 college students, including complete roentgenologic studies of the teeth. Although 19.8 per cent of the group had periapical areas of rarefaction, no statistically significant association with systemic disease could be demonstrated. The areas of rarefaction were not associated with rheumatism, chorea, or heart disease. From a review of the literature and upon the basis of their own study, the authors conclude that: "The wholesale removal of devitalized teeth and teeth with granulomata is certainly without justification in healthy young individuals."

## III. HISTOLOGIC STUDIES

Histologists who have studied sections of pulpless teeth are agreed, almost without exception, upon three things: (1) that periapical bone restoration can and often does follow satisfactory root canal treatment of pulpless teeth; (2) that such pulpless teeth are commonly without histologic evidence of infection; and (3) that they may be safely retained in the mouth. It is interesting also to note that of 250 roentgen-ray negative pulpless teeth, Skillen<sup>15</sup> found evidence of infection in only six upon histologic examination.

## IV. BACTERIOLOGIC STUDIES

The most indicting evidence against the pulpless tooth as a focus of infection has come from the bacteriologic laboratory. The two outstanding studies in the field of dental focal infection, considering both the quantity and quality of material studied, are probably those of Haden<sup>16</sup> and of Burket.<sup>17</sup> The data are particularly valuable for comparative analysis because Haden used one method of study and Burket another. Burket used the "external approach" method, which consisted in aseptically laying bare the alveolar tissues and making a culture direct from the root apex while the tooth was still in situ. Haden first extracted the tooth and then made

cultures from the root end. Burket reported results on 429 teeth, and Haden on 1500 teeth. Haden obtained growth from 87 per cent of pulpless teeth and from 55 per cent of vital teeth; Burket obtained growth from 72 per cent of pulpless teeth and 43 per cent of vital teeth. These findings run fairly close together considering the fact that the methods differed and the material was not identical. This important observation may now be made: If the vital teeth are used as controls, the difference between the percentages of growth found in the pulpless and in the vital teeth will then give us the actual percentage of growth found in pulpless teeth (see figure 2). Since,

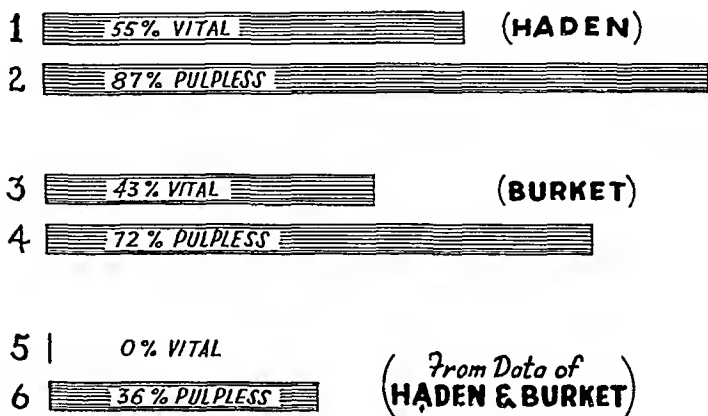


FIG. 2. (1-4) Per cent of growth from vital and from pulpless teeth obtained by Haden and by Burket. When per cent of growth from vital teeth (5) is taken as normal, the growth from pulpless teeth (6) is only 36 per cent.

in the combined data of Haden and Burket, the weighted average for growth from pulpless teeth is 85 per cent, and the weighted average for growth from vital teeth is 49 per cent, the difference, or 36 per cent, is probably nearer the *actual* percentage of growth found in pulpless teeth. If we add to this the fact that the pulpless teeth studied by Haden and Burket were treated a number of years ago, when root canal therapy was not so satisfactory as it is today, and that the finding of bacterial growth in cultures from teeth does not necessarily imply the presence of infection, the bacteriologic evidence against the pulpless tooth is not so damning.

#### RECENT INVESTIGATIONS

A new interpretation of past studies on the pulpless tooth must be given in the light of recent studies by Fish and MacLean,<sup>18</sup> Okell and Elliot,<sup>19</sup> and Gunter and Appleton.<sup>20</sup> These studies practically compel one to scrap all previous bacteriologic studies dealing with pulpless teeth.

An important study, destined to have a far-reaching influence upon the interpretation of the bacteriologic status of pulpless teeth, was reported by Fish and MacLean<sup>18</sup> in 1936. They had made the observation that, despite the fact that a great many investigators recovered bacteria from living pulps, both the pulps and periapical tissues of vital, healthy teeth were invariably

free of any evidence of bacteria or irritation when examined histologically. They therefore wondered whether the microorganisms gained access to the pulp during extraction and arrived too late to set up a reaction. This supposition was strengthened by a study reported by Okell and Elliot,<sup>19</sup> who recovered mouth organisms from circulating blood within a few minutes after extraction of a pyorrheic tooth, even though the blood was sterile immediately before and again some time after the extraction. Apparently sufficient trauma was present during the act of extraction to force organisms into the blood stream, there to produce a transient bacteremia. The question then arose as to whether these organisms were present in the periapical tissues before extraction or whether they came from the pyorrheic pocket. They reasoned as follows: "If our view were correct, provided we sterilized the pocket before extraction, we should always get a sterile apex, a sterile pulp and sterile blood stream after extraction; but if we were wrong and if the organisms were indeed living freely among the cells in the periapical tissues and in the pulp, our sterilization of the pocket would make no difference and after extraction we should still find the apex and the pulp infected and the patient would have the usual transient bacteremia which Okell and Elliot had discovered, and which we had ourselves confirmed." This question Fish and MacLean set out to settle, and found that the organisms came from the debris in the pyorrheic pocket despite attempts to sterilize the pocket by means of antiseptics. Only when the pocket was cauterized with a red hot cautery did they succeed in preventing a transient bacteremia. They thus proved that bacteria were "pumped" into the blood and lymph channels during manipulation of the tooth while it was being extracted. They found further that streptococci are present only in necrotic areas of bone and do not diffuse through the granulation tissue (if it be present) about the root apex. Such streptococci are only transient migrants in the environment of living tissue and require necrotic material in which to grow. In grossly infected pulpless teeth the infection is limited to the root canals or can be found in the pus of the associated abscess. Even in such cases the neighboring alveolar bone and soft tissues are sterile, although they may be irritated by the diffusion of toxic products. The importance of the work of Fish and MacLean lies in the fact that they have shown that it is practically impossible to remove a tooth aseptically (without actual cauterization of the gingival crevice) because bacteria are forced into the pulp and periapical tissues during the act of extraction.

Experimental evidence that bacteria are capable of being "pumped" into a tooth during extraction is given by Kanner,<sup>21</sup> who attempted to copy in vitro the mechanism of pumping or sucking bacteria into pulps of extracted teeth by way of the apical foramen. The method consisted of placing a freshly extracted tooth into a lateral bulge or pocket blown in a test tube. In the bottom of the tube was a suspension of *B. sporogenes*, an easily identifiable organism. The tube was connected to a vacuum pump and the pressure was lowered to about one-half atmosphere. The tube was then

tilted so that the tooth dropped into the bacterial suspension and the atmospheric pressure was then restored to normal. The tooth was removed from the tube, the surface cleansed mechanically, sterilized after the method of Tunncliffe and Hammond,<sup>22</sup> then placed in nutrient gelatin and incubated under anaerobic conditions. In all cases in which the bacterial suspension had been "pumped" into the pulp the same organism grew out of the apical foramen. In addition, histologic sections showed the presence of these organisms within the pulps of the "pumped" teeth. From these experiments Kanner concluded that pressure (or suction) is capable of causing bacteria to enter the pulp and that such a mechanism may be operative during extraction, particularly during luxation of the tooth from its socket when spaces are opened up which are capable of admitting microorganisms from the neighborhood.

Evidence that even the best bacteriological technic cannot prevent the risk of contamination during extraction is further given by Tunncliffe and Hammond<sup>22</sup> who found streptococci in the pulps of intact, vital teeth even after adequate surface sterilization. Their method was as follows: Teeth were placed in 88 per cent phenol for 15 minutes, washed in alcohol, flamed, left in alcohol for 15 minutes and flamed again. The teeth were then cultured for eight days in glucose-brain broth to determine sterility. Thirty teeth showing no surface growth were then opened aseptically, and smears, sections and cultures of the pulp were made. In 10 cases growth was obtained even though the teeth used in the study were externally intact and sterile. Histologic sections of the pulps showed no signs of infection, and Tunncliffe and Hammond concluded from this study that their "findings are in accord with those of Fish and MacLean that, histologically, streptococci may be demonstrated in pulps of intact teeth without any evidence of infection."

Indirectly supporting the work of Fish and MacLean are the studies of Okell and Elliot,<sup>19</sup> and of Burket and Burn.<sup>23</sup> As has already been mentioned, Okell and Elliot took blood cultures before, and then 10 minutes after, extraction of teeth which were removed under general anesthesia. Positive blood cultures were obtained in more than 60 per cent of cases after extraction, though cultures were negative before extraction. When a local anesthetic, containing a vasoconstrictor, was substituted for general anesthesia, Burket and Burn obtained fewer positive cultures. Transient bacteremias occurred, nevertheless, in 17 per cent of cases, even despite capillary constriction from the epinephrine contained in the local anesthetic solution.

#### DISCUSSION

Inasmuch as the recovery of bacteria from the blood stream following tooth extraction is an indication that dissemination of bacteria from the dental tissues has occurred, and since there is evidence that in a great many cases contamination of the root surface or of the pulp occurs during extraction, the significance of finding growth within the pulp or upon the surfaces

of extracted pulpless teeth must be questioned. That the entire chapter on the bacteriology of vital and pulpless teeth needs to be rewritten is further evidenced by the fact that recent studies on the bacteriology of the living, healthy pulp are at variance with those of the past.

Practically every investigator who has, at one time or another, studied the bacteriology of the vital pulp has found growth present in a greater or lesser percentage of cases. Haden<sup>10</sup> believed that chronic infection occurs quite commonly in the pulps of vital teeth and went so far as to say that "many believe there is a chronic infection in the pulp of every tooth in which the dentin is invaded by caries." If this were taken literally and such teeth were condemned, we should have a toothless nation, since it is estimated that more than 90 per cent of the people have carious teeth or have had carious teeth at one time. In the light of studies by Fish and MacLean, and by Okell and Elliot, it is easy to understand why bacteria were recovered from normal, healthy pulps following tooth extraction. When vital pulps were exposed and cultured in situ according to the method of Gunter and Appleton,<sup>20</sup> whereby contamination from the gingival crevice is eliminated, no growth was obtained. This again points to the fact that in previous studies of vital teeth, bacteria were forced into the pulps during extraction, which gave an erroneous indication of the bacteriologic status of such teeth. By the same token, bacteria were forced within or upon the surfaces of extracted pulpless teeth, from the cultures of which growth was afterward recovered. Cultures made from extracted teeth do not, therefore, reflect the true bacteriologic status whether it be of vital or of pulpless teeth, unless, as shown by Fish and MacLean, the gingival tissues are first cauterized. Since pulpless teeth fell somewhat into disrepute because of bacteriologic studies made in the last 15 or 20 years, and since the findings were generally based upon bacteriologic examinations made after extraction, without adequate means having been taken to prevent contamination, past interpretations can no longer be held valid in the light of recent knowledge. We must look to recent and future investigations rather than those of the past, to determine the bacteriologic status of the pulpless tooth. *From what is already known it is expected that such investigations will be in closer agreement with correlative studies already made of pulpless teeth by clinical, roentgenologic and histologic examinations.* To hold the pulpless tooth to the bacteriologic criticism of the past would seem unjustified.

#### SUMMARY

1. A pulpless tooth is not a "dead" tooth. It still continues to have a vital relationship with the surrounding tissue.
2. The more important clinical, roentgenologic, histologic and bacteriologic studies dealing with the pulpless tooth as a possible focus of infection have been reviewed and evaluated. The accumulated evidence against the pulpless tooth, even at its worst, is not so damning. Actually, growth from pulpless teeth was recovered in about 36 per cent of cases when compared

with growth recovered from vital teeth. Recovery of growth, per se, does not indicate that infection was present.

3. Recent bacteriologic studies dealing with the pulpless tooth have been presented. These studies tend to invalidate, to a great extent, the results of previous investigations, or to interpret them in a new light.

4. In view of the evidence presented, indiscriminate extraction of pulpless teeth is unwarranted.

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# A CORRELATION STUDY BETWEEN RETINAL VASCULAR CHANGES, ELECTROCARDIOGRAPHIC ALTERATIONS AND RADIOLOGICAL HEART SIZE IN ESSENTIAL HYPERTENSION \*

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## INTRODUCTION

IN essential chronic hypertension the relative simplicity of diagnosis stands in striking contrast to the more difficult problem of prognosis. It is well known that the ultimate fate of individuals exhibiting this condition is determined by the cardiovascular diseases consequent to the hypertension, the most important of which are the cardiac hypertrophy and the arterial or arteriolar sclerosis. These changes are of particular significance when the arterioles of the brain, kidneys, myocardium and retina are involved. It is also well known that death will usually result from myocardial failure, although cerebral hemorrhage, myocardial infarction and uremia are frequent terminal events. Occasionally dissecting hemorrhage of the aorta may occur. Apart from these generalizations the problem of prognosis has been discussed in the literature more specifically with reference to various clinical manifestations, kidney function and height of blood pressure. Of the more recent objective evidence of this disease, retinal vascular changes and electrocardiographic abnormalities have been given relatively little consideration. Furthermore it has been the practice in many studies to determine heart size by palpation and percussion instead of by the more accurate roentgenologic (orthodiagraphic) method. The studies dealing with prognosis have been determined by grouping the various criteria and recording the number of individuals in each group alive at some chosen time. Since so little attention has been paid to the possibility of utilizing the material obtained from objective experience, we have undertaken to determine some of the facts in regard to the retinal vascular changes, electrocardiographic alterations and the radiological heart size in a group of patients with essential hypertension. Special attention was given to the frequency, the type and the degree of the changes and particularly to their correlation and relative value. Although the selected material in this study is numerically inadequate for a comprehensive statistical compilation, it seems sufficient to suggest a definite trend which more study would probably establish as a fact.

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## MATERIAL

In order to obtain uncomplicated cases of essential hypertension those cases in which one or more of the following conditions were present were eliminated: (1) glomerulonephritis, advanced prostatism, syphilis, diabetes, thyrotoxicosis, anemia (exception: one case had a moderate degree of secondary anemia), coarctation of the aorta, cardiac infarction, valvular disease (exception: one case had an atherosclerotic mitral regurgitation); (2) (from an electrocardiographic viewpoint) QRS complex larger than 0.10 sec., auricular fibrillation, evidence of cardiac infarction, old or recent; (3) digitalis medication within the three weeks preceding the electrocardiographic study. From a series of 500 cases which were studied it was necessary to exclude 420 patients because they had one or more of the above complicating conditions. The remaining 80 cases included 38 males and 42 females; the youngest patient was 12½ years of age, the oldest 73 years of age, with 55 per cent of all the cases between 40 and 59 years of age. The selected patients had a diastolic blood pressure of at least 95 mm. Hg and a systolic pressure of at least 150 mm. Hg. All of the cases had electrocardiographic and retinal studies, but unfortunately 21 cases were too ill to have a fluoroscopic and orthodiagraphic study done, which leaves 59 cases in which an orthodiagraphic study was undertaken. The question of the duration of the hypertension has been one factor we have been unable to ascertain with accuracy.

The reports on the fundi examinations, from which our study has been made, are based on the description and grouping of Wagener.<sup>1</sup> It seems desirable to quote his presentation of the subject:

As seen with the ophthalmoscope, the first alterations that take place in the arterioles of the retina are narrowing of the caliber, a change to a lighter color than normal of the entire breadth of the arteriole, and exaggeration and broadening, or accentuation, of the reflex stripe. These are regarded by some as signs of hypertension in the sense of spastic arteriolar constriction or increased arteriolar tonus and by others as the commencement of actual arteriosclerosis through thickening of the media.

(In our study these cases have been classified as preorganic or pre-sclerotic. It is thought that the retinal arterioles have been subjected to increased pressure of insufficient duration or intensity to cause sclerosis.)

In more advanced cases, signs of definite sclerosis appear, irregularities of the lumen of the arterioles, compression of the veins at the arterial crossing and at times visibility of the vascular walls. Irregularity of lumen is the most definite sign of sclerosis, if it is not confused with the irregularity produced by spasm. Sclerosis observed in advanced cases is visible in all branches, but in earlier stages is best seen in the smaller arteries, either in the nasal or in the secondary and tertiary branches of the temporal vessels. It is usually rather evenly distributed in grade in all vessels of approximately the same size. Severity of sclerosis can be graded from 1 to 4, largely on the basis of the number of irregularities, and the degree to which they narrow the lumen of the arterioles.

If the narrowings are just barely perceptible, the case is classified as

grade I sclerosis (figure 1). If the narrowings are more numerous and cause rather obvious encroachment on the lumen, the sclerosis is classed as grade II (figure 2). If there is marked narrowing and marked caliber

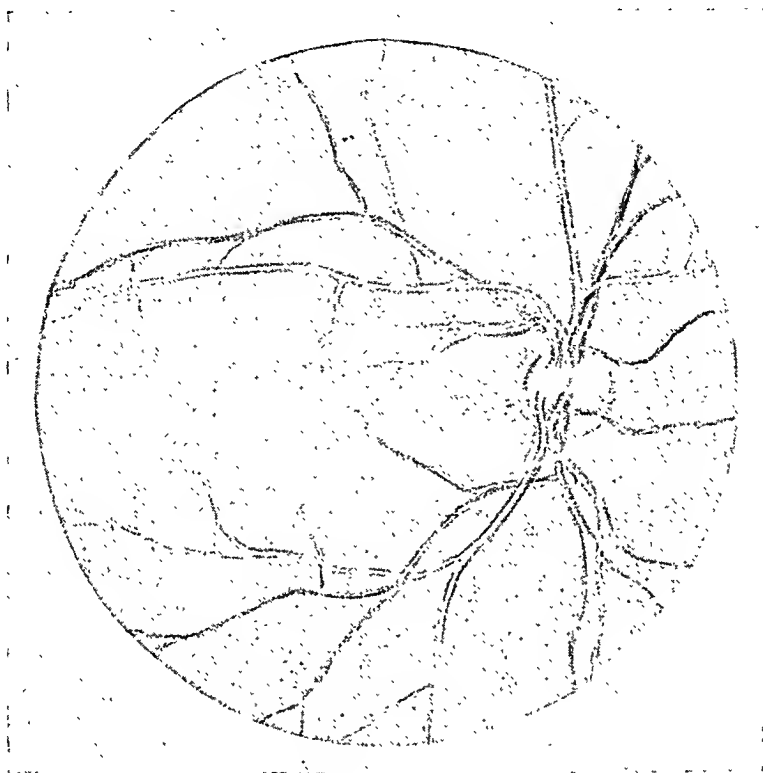


FIG. 1. Fundus picture in the presence of grade I sclerosis.

diminution, the sclerosis is classified as grade III (figure 3). If the arteriole is so reduced in caliber as to appear as a white line, this is the maximum amount of sclerosis and is said to be grade IV.

Since there is no complete agreement about the preorganic group of arteriolar constriction, we have included in our group designated as I in the tables those cases which we classified ophthalmoscopically as the preorganic group and the mildest (grade I) sclerosis.

The electrocardiographic studies were evaluated for the presence or absence of left axis deviation and aberrations of the final deflection. An alteration of the R (S) T interval level was considered significant if the deviation was equal to or greater than  $\frac{1}{2}$  millimeter from the base line. Since in these series we are not dealing with instances of tachycardia, the T-P level has been taken as the base line. This R (S) T interval is often depressed in Lead I, or I and II, and often elevated in Lead III. The shape has also been considered—such as straight, oblique or arched. T-wave changes were considered with reference to direction and amplitude. They may be negative or diphasic in Lead I, or I and II, and may resemble the cove plane type of T-wave observed in the course of myocardial infarction.

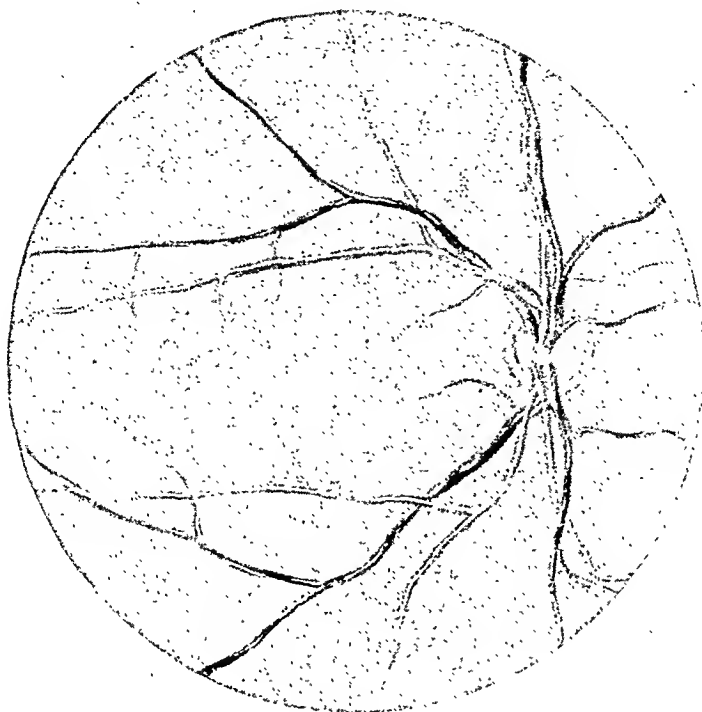


FIG. 2. Fundus picture in the presence of grade II sclerosis.

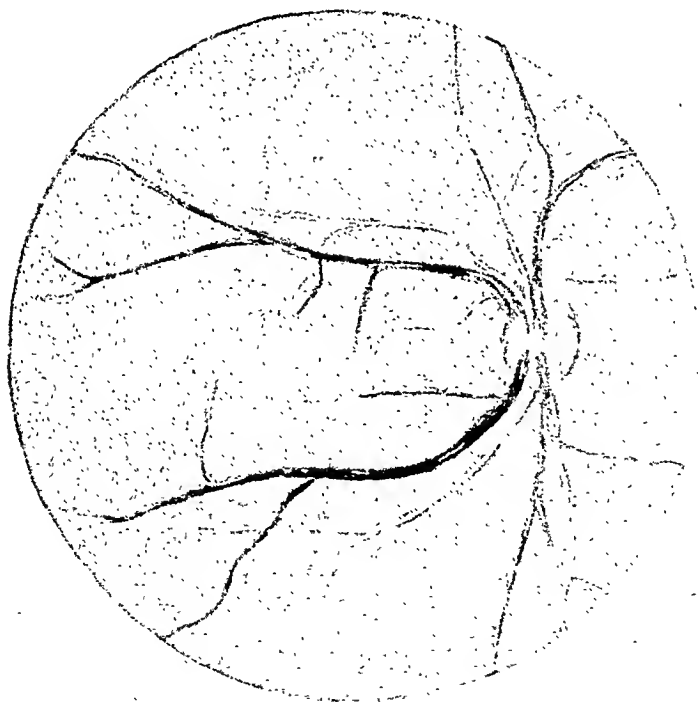


FIG. 3. Fundus picture in the presence of grade III sclerosis.

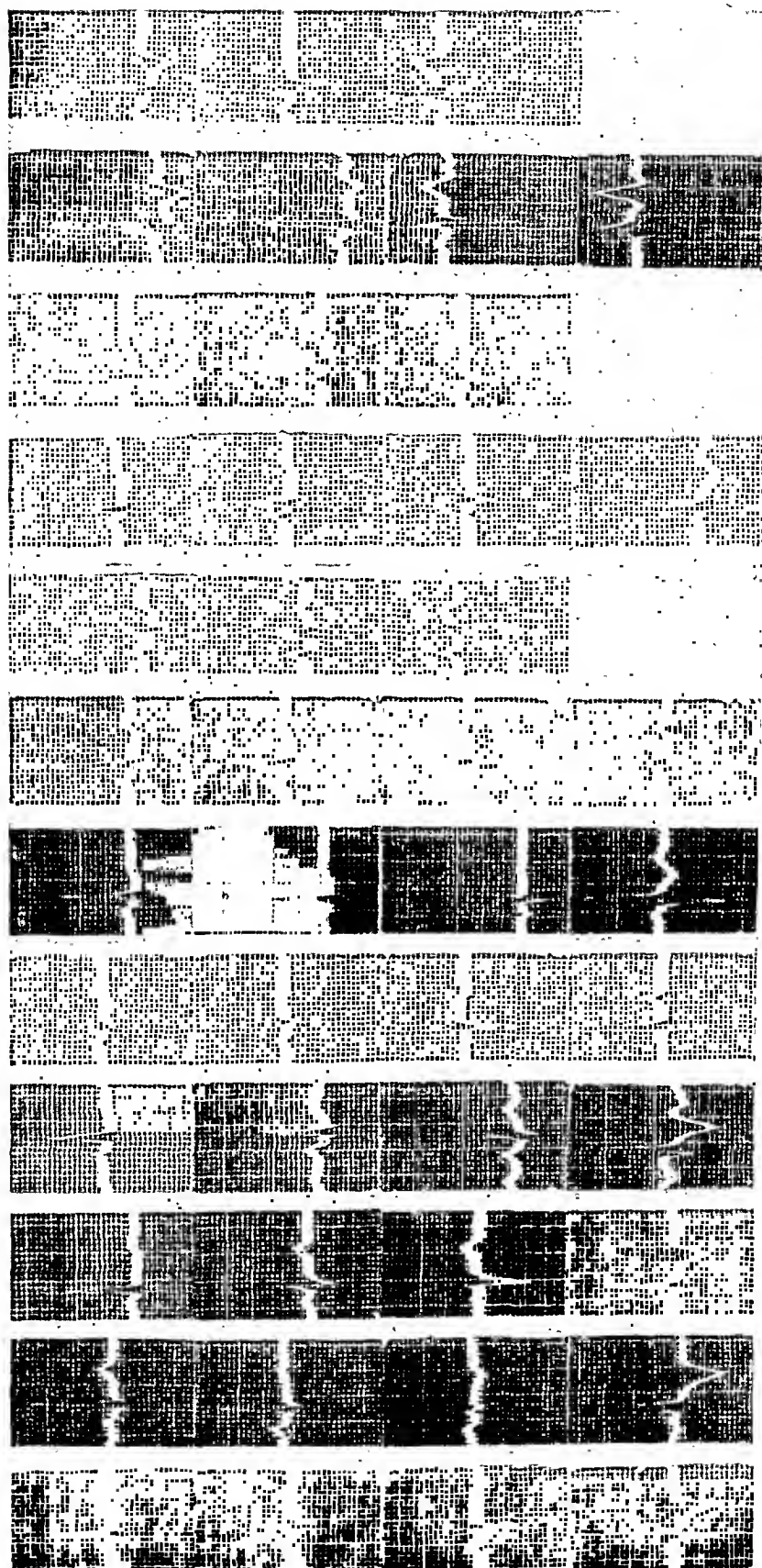


FIG. 4.

The heart size was determined by orthodiagrams. The size of the patient's chest and of his clenched fist was found to be valuable for the crude but practical subdivision into normal, slightly to moderately, and markedly enlarged.

We have found, as one might expect, a variety of combinations of final deflection changes in the electrocardiograms. Samples of these, selected at random, demonstrating different types, are illustrated in figure 4. A comparison of the three criteria, i.e., retinal vascular changes, electrocardiographic alterations and heart size, impresses one with a certain lack of correlation which will be discussed shortly.

### DATA

The data have been arranged in three tables. The association of electrocardiographic findings with retinal changes is shown in table 1. The association of radiologic findings, as to cardiac size, with retinal changes is shown in table 2. In table 3 the data are arranged to show the association between the electrocardiographic and the radiologic findings.

### RESULTS

(1) The fundus examination revealed retinal arteriolar changes, hypertensive type, in all of the 80 cases, with 88.8 per cent (71 cases) classified as having advanced to the stage of sclerosis, and with the remaining 11.2 per cent in the preorganic stage of the disease.

(2) The electrocardiographic study gave the following results. Final deflection changes were present in 68.8 per cent (55 of the 80 cases). Left axis deviation occurred in 75.0 per cent (62 cases). Final deflection changes were associated with left axis deviation in 57.4 per cent (46 cases), while left axis deviation occurred without associated final deflection changes in 20.0 per cent (16 cases). In 11.3 per cent (9 cases) the ECG was en-

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FIG. 4. Samples of electrocardiograms from 12 cases, left to right. From above down Leads I, II, III, IV (left arm lead to electrode in left interseapular space, right arm lead to apical electrode).

(1) aged 55, no failure, but dyspnea on effort, B. P. 220-120, heart slightly enlarged. Fundi: grade I sclerosis, marked angiospastic features. (2) aged 51, no failure, B. P. 160-105, heart slightly enlarged. Fundi: grade I sclerosis. (3) aged 50, slight degree of failure, B. P. 240-110, heart moderately enlarged. Fundi: grade II sclerosis with retinitis of severe benign hypertension. (4) aged 46, no failure, B. P. 180-125, heart slightly enlarged. Fundi: marked vasospastic changes in retinal arterioles. (5) aged 50, no failure (angina pectoris), B. P. 200-140, heart normal in size. Fundi: grade I sclerosis and vasospastic changes. (6) aged 67, slight degree of left-sided failure, B. P. 220-155, heart moderately enlarged. Fundi: sclerosis grade II with retinitis of malignant hypertension. (7) aged 47, no failure, B. P. 185-95, heart moderately enlarged. Fundi: grade I sclerosis and preorganic vasospastic changes. (8) aged 32, no failure, B. P. 195-145, marked cardiac enlargement. Fundi: grade I sclerosis with vasospastic retinitis. (9) aged 51, very slight failure, B. P. 230-130, moderate degree of cardiac enlargement. Fundi: grade II sclerosis with retinitis of malignant hypertension. (10) aged 58, case with skull fracture, B. P. 235-135. Fundi: grade II sclerosis with retinitis of severe benign hypertension. (11) aged 50, no failure (asthmatic bronchitis), B. P. 180-105, heart moderately enlarged. Fundi: grade I sclerosis. (12) aged 52, angina pectoris and nocturnal dyspnea, B. P. 200-100, heart markedly enlarged. Fundi: grade I sclerosis and vasospastic changes.

tirely normal, as no final deflection changes or left axis deviation were present. Since left axis deviation may also occur, so to speak, physiologically with a certain constitutional type and in the higher age group, it cannot be considered as necessarily significant. Hence, in 31.3 per cent (25 cases) the electrocardiogram revealed no significant findings.

(3) The orthodiagraphic study of 59 cases showed absence of cardiac enlargement in 22 per cent (13 cases); a slight to moderate enlargement was present in 50.8 per cent (30 cases), and a marked degree of enlargement occurred in 27.1 per cent (16 cases).

### STATISTICAL EVALUATION

Since the selected material is not large, any statistical discussion can be based only upon the trends of the data present. It is assumed that with a greater number of cases the distribution would remain relatively the same. This assumption is subject to verification by a more extensive research.







*Method.* As units, electrocardiographic findings were classified as either non-pathological, when there was no final deflection change (FDC), or as pathological, when there was a final deflection change. Data as to left axis deviation (LAD) are included for completeness. Retinal changes were classified as groups I, II and III arteriolosclerosis hypertensive type. Group I includes cases with narrowing of the arterioles, with increased intensity of the reflex stripe but without constriction. Cardiac enlargement was classified as none, moderate and marked. Tables 1 and 3 consist of division into six sections, and table 2 consists of division into nine sections, for a paired comparison of each clinical manifestation with the other, respectively. The material was distributed in classification boxes. Thus, for example, in table 1 the number of cases showing grade I retinal arteriolosclerosis and absent final deflection changes in the electrocardiogram have been put into one box; those showing grade I changes with final deflection changes into another box, etc. Each of the horizontal rows has been totaled, and the percentage of each class has been computed; this percentage has been plotted as a divided horizontal bar, so that regardless of the number of cases the relative lengths of the bars indicate the distribution into the three classes indicated. The sums of these horizontal bars have been treated in the same way, giving an additional horizontal bar, indicative of the average distribution of these selected cases. Each of the vertical columns has been likewise totaled, and the percentage of each class has been computed. This percentage has been plotted as a divided vertical bar, so that regardless of the number of cases the relative lengths of the bars indicate the distribution into the two classes (tables 1 and 3) and into the three classes (table 2), respectively. The sums of these vertical bars have been treated in the same way, giving an additional vertical bar, indicative of the average distribution of these selected cases.

*Analysis.* Table 1 (80 cases): The horizontal bars indicate an increase

of groups II and III retinal arteriosclerotic changes, hypertensive type, in cases with electrocardiographic final deflection changes, as compared to the average (lower right hand corner), and as compared to the cases with ab-

TABLE I

Relative distribution of electrocardiographic versus ophthalmoscopic findings in essential hypertension (80 cases).

E.C.G. ALTERATIONS	RETINAL CHANGES				
	I	II	III		
F.D.C. ABSENT	16	8	1		64/32/4 %
L.A.D. ABSENT	6	3	0		
L.A.D. PRESENT	10	5	1		
F.D.C. PRESENT	24	24	7		44/44/12 %
L.A.D. PRESENT	19	23	4		
L.A.D. ABSENT	5	1	3		
AVERAGE E.C.G. ALTERATIONS					AVERAGE RETINAL CHANGES 50/40/10 %
	31 69 %	40 60 %	25 75 %	12 88 %	

Abbreviations in this and the following tables: F.D.C.: final deflection changes; L.A.D.: left axis deviation. I, II, III: grades of retinal arteriolar sclerosis, hypertensive type; I includes cases with narrowing of the arterioles, with increased intensity of the reflex stripe but without constriction.

sence of final deflection changes. The vertical bars indicate a steady increase in the percentage of cases with electrocardiographic final deflection changes as the retinal examination shows an increasing grade of retinal vascular pathology. There are definitely noticeable exceptions to this positive correlation as shown in those hypertensive patients who reveal an association of final deflection changes, without left axis deviation, together with a lesser degree (group I) of retinal arteriolar sclerosis (five cases, first row, second column). Conversely, one finds that an absence of final deflection changes, with left axis deviation, is compatible with a high degree (group III) of retinal changes (one case, third row, first column). Conclusion: There is a trend towards a positive correlation between retinal vascular changes and electrocardiographic alterations.

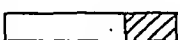
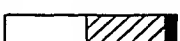
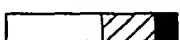




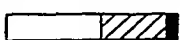
Table 2 (59 cases): The horizontal bars indicate an increase of group III, retinal arteriolar sclerosis hypertensive type, with progressive change in heart size. The progression for group II is not regular. However, if one fuses the rows for moderate and marked cardiac enlargement, the increase for group II is quite striking, both as compared to the average (lower right hand corner) and as compared to the percentage of cases with normal heart size. The vertical bars indicate in general an increase in



cardiac enlargement together with progression in retinal vascular sclerosis. Certainly, as retinal pathologic changes increase the incidence of no cardiac enlargement is progressively reduced, and in our series normal heart size

TABLE II

Relative distribution of radiologic versus ophthalmoscopic findings in essential hypertension (59 cases).

CARDIAC ENLARGEMENT	RETINAL CHANGES					
	I	II	III			
NONE	10	3	0		77/23/0 %	
MODERATE	14	14	2		47/47/6 %	
MARKED	9	5	2		56/31/13 %	
AVERAGE CARDIAC ENLARGEMENT						56/37/7 %
	$\frac{22}{51}$ 27 %	$\frac{30}{43}$ 27 %	$\frac{13}{64}$ 23 %	$\frac{0}{50}$ 50 %		







does not happen to coincide with group III, retinal arteriolosclerosis, hypertensive type (third row, first column). Exceptions to this positive correlation are shown in those hypertensive patients who have an association of normal radiological heart size with a higher degree (group II) of retinal arteriolosclerosis (three cases, first row, second column). The degree of correlation would presumably be greater except for the fact that 21 patients were too ill to permit a fluoroscopic study; 14 of these fell into retinal arteriolosclerosis groups II and III. Conclusion: There is a trend towards a positive correlation between cardiac enlargement and the grade of the retinal arteriolar changes.

Table 3 (59 cases): The horizontal bars indicate an increase of cardiac enlargement in cases with electrocardiographic final deflection changes, as compared to the average (lower right hand corner), and as compared to the cases with absence of final deflection changes. The vertical bars indicate a steady increase in the percentage of cases with electrocardiographic final deflection changes as the radiologic examination shows an increase in the size of the heart. Again it is possible for hypertensive patients to show an association of final deflection changes, without left axis deviation, together with a normal heart size (two cases, first row, second column). Conversely, one finds that an absence of final deflection changes, and of left

axis deviation, is compatible with a marked degree of cardiac enlargement (two cases, third row, first column). Conclusion: There is a trend towards a positive correlation between electrocardiographic changes and cardiac enlargement.

TABLE III

Relative distribution of electrocardiographic versus radiologic findings in essential hypertension (59 cases).

E.C.G. ALTERATIONS	CARDIAC ENLARGEMENT			
	NONE	MOD- ERATE	MARKED	
F.D.C. ABSENT L.A.D. ABSENT L.A.D. PRESENT	6 5 1	11 6 5	3 2 1	 30/55/15 %
F.D.C. PRESENT L.A.D. PRESENT L.A.D. ABSENT	7 5 2	19 16 3	13 11 2	 18/49/33 %
AVERAGE E.C.G. ALTERATIONS				 22/51/27 % AVERAGE CARDIAC ENLARGEMENT
	$\frac{34}{66}$ %	$\frac{46}{54}$ %	$\frac{37}{63}$ %	$\frac{18}{82}$ %

### DISCUSSION

An attempt will be made to discuss the three criteria and their incomplete correlation by presenting some essential data and giving those references which will be of interest to the student of these problems.

*Vascular Changes in General.* In any discussion of hypertension it is necessary for one to consider the pathological changes in the blood vessels. In this regard some significant facts are revealed by a perusal of the literature and from personal observations. Arteriosclerosis is found in association with hypertension, particularly in the kidneys. However, this is merely an aggravation of a process which is present already in non-hypertensive individuals. This process is irregularly distributed in the body in general and may be segmental in arrangement within a vessel.<sup>2, 3, 4, 5, 6, 7</sup> In the heart these lesions are often but moderate in intensity or insignificant altogether and have neither a relation to the degree of the atherosclerosis in the main branches of the coronary arteries nor to the degree of fibrotic scarring in the heart muscle.<sup>4, 8, 9, 10, 11</sup> Such discrepancies in the distribution of the arteriosclerotic process have been pointed out for the retinal vessels likewise, by comparing the findings in the central retinal artery with those in the retinal arterioles,<sup>12, 13</sup> or the retinal arterioles among themselves.<sup>14</sup> That there is no strict parallelism between changes in the retinal vascular tree and the arteriosclerosis of the larger peripheral vessels,<sup>15, 16, 17, 18</sup> or of the larger basal cerebral vessels<sup>19, 20</sup> has been demonstrated.

*Retinal Vascular Changes.* Classical ophthalmoscopic descriptions have been given in the last century.<sup>15, 21, 22</sup> The significance of arteriolar disease as a basis of the so-called albuminuric retinitis has likewise been recognized,<sup>23, 24</sup> while later on the ophthalmoscopic characteristics of the arteriosclerotic<sup>25</sup> and of the ischemic, angiospastic<sup>26, 27</sup> retinitis have been described. For the details, we refer to some of the more recent excellent publications.<sup>28, 29, 1, 30, 31</sup>

Associated with vascular sclerotic changes there may occur in the retinal tissues hemorrhages, edema, and finally, in association with spastic changes in the vessels, ischemia and focal necrosis. The occurrence of various combinations of such lesions has been referred to as retinitis, although the processes are quite different from those usually designated as inflammation. Retinitis of hypertension may occur in the preorganic phase of the disease when the severity of the lesion progresses from increased arteriolar tonus to actual spasm of the vessel. Retinitis seldom occurs with grade I sclerosis, occasionally with a grade II, usually with a grade III, and almost invariably at some time in the course of a grade IV sclerosis. The presence of a retinitis adds a definite element of gravity to the prognostic picture.

Systemic hypertension may diminish or even disappear, particularly so in the course of cardiac failure. This fall is usually more marked for the systolic than for the diastolic pressure. Retinal arteriosclerosis, however, persists and is then an important diagnostic sign, indicating that the patient had previously had hypertension.<sup>18, 32</sup>

It is thought that the degree of retinal arteriolosclerosis depends upon the degree and the duration of the hypertension. Although it is true that an elevation of the peripheral blood pressure, as determined in the brachial artery, is accompanied by an elevation in the pressure of the central retinal artery at the level of the disc, as determined by Baillart's dynamometer (tonoscopy), yet it has been shown that between them there exists no close parallelism. The principle of tonoscopy consists in steadily increasing outside pressure on the bulb. At a certain level of pressure the motionless central artery shows a tremor, and this indicates the moment when the diastolic pressure is equalized. The artery then is seen to empty and fill itself rhythmically, and finally the pulse just before the complete collapse indicates the systolic pressure. The diastolic retinal pressure can always be determined while the measurement of the systolic pressure has its limit at about 150 mm. Hg. Several investigators have published data revealing a rather wide range in the ratio of the diastolic retinal to the diastolic brachial pressure.<sup>33, 34, 35, 36</sup> In a series of 20 cases the ratio varied from 0.30 to 0.96,<sup>33</sup> and from 0.48 to 0.84 in another study comprising 31 cases.<sup>35 \*</sup> If it is assumed that the tension in the retinal arterioles is an important factor in the development of arteriolosclerosis, it is of great significance that there is not necessarily a close parallelism between peripheral and retinal blood pressure.

\* We have determined this ratio for those cases in which the diastolic pressure was 95 mm. Hg or more.

This perhaps might explain why we observe, though rarely enough, the absence of arteriolosclerotic changes in the eyes of patients who are known to have a typical essential hypertension of the non-intermittent type.

Figures pertaining to the frequency of retinal arteriolar changes in the presence of essential hypertension vary considerably.<sup>18, 37, 38, 39, 8, 40, 41, 42, 43, 44, 45, 46</sup> A detailed study of these reports reveals that one cause for the difference in frequency of pathological changes is due to differences in the criteria used. It seems quite likely that early changes have been overlooked and hence a relatively high percentage of normal eyegrounds has been reported. The study of the retinal arterioles demands inspection from the disc to the extremes of the arteriolar tree through a dilated pupil. Another reason for varying statements is the fact that cases with increased systolic but normal diastolic blood pressure (or even without statements as to the latter) were included in some such studies. In two very careful investigations<sup>39, 41</sup> the frequency of an abnormal fundus picture was found to be as high as 96 per cent and 93 per cent respectively.

*Electrocardiographic Changes.* Left axis deviation, increased amplitude of the initial deflection, and abnormalities of the final deflection are often, though not regularly, found in association with hypertensive heart disease.<sup>47, 48, 49, 50, 44, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60</sup> Final deflection changes may well be sequelae to bundle branch block, myocardial infarction, or digitalis medication, and in some of the publications, these factors have not always received the attention which they warrant. It is not entirely clear at the present time what the rôle is of the hypertrophy, dilatation, or myocardial damage, in affecting the metabolic activity of the myocardium to produce these final deflection changes. An outlasting of the excitation rather than a delay, for the left ventricle, has been suggested.<sup>61</sup> The electrocardiographic pattern of left axis deviation, with final deflection changes in Lead I, or Leads I and II, has been correlated with the clinical picture,<sup>49, 58</sup> or with mortality rate,<sup>55, 53, 59</sup> or with both.<sup>56</sup> Also, T-wave negativity has been considered exclusively.<sup>50</sup> The general trend has been to ascribe to these findings a serious prognostic significance. Such a general statement is not justified in our experience. The finding indicates an advanced degree of left ventricular hypertrophy with strain but it does not seem sufficient to warrant a diagnosis of severe myocardial damage. Cases have been reported in which the aforementioned electrocardiographic pattern has been observed, and later a careful postmortem examination revealed no macroscopic evidence of coronary artery sclerosis.<sup>52, 60</sup>

*Heart Size.* The radiological evaluation of heart size gives more reliable results than those obtained by means of percussion and palpation, and that this holds particularly true for the obese and emphysematous needs no further discussion. A considerable degree of hypertrophy is compatible with a normally sized cardiac silhouette. Experience shows that heart size is not more than a fair criterion as to effort capacity and expectation of life, and that this criterion is of greater value in valvular disease of rheumatic

etiology than in the group of hearts with coronary artery disease.<sup>62</sup> For a complete evaluation of the prognostic significance of heart size it is necessary to know if congestive failure exists or has existed with particular reference to pulmonary congestion.

Whereas all fundi revealed at least some degree of vascular change, we find that 11.3 per cent of all cases had a perfectly normal electrocardiogram; if we exclude left axis deviation as evidence of abnormality, 31.3 per cent had a non-significant electrocardiogram. Furthermore 22 per cent showed a normal radiological heart size. The ophthalmoscopic examination, therefore, gave the highest incidence of positive findings in these carefully selected cases.

The incomplete correlation is in part explainable by the fact that no attempt was made in this study to arrange the data on the basis of the duration of the disease and the severity of the hypertension. Obviously, certain cases lack the elements of intensity or duration of their condition to bring about evidence of the disease in the electrocardiogram or roentgenogram.

The correlation between each of these criteria has not been demonstrated to be of high statistical significance. The relatively small number of cases has not permitted the computation of the coefficient of correlation.

Prognostication can be better made when follow-up studies of the three criteria are available after the elapse of several years. In view of the fact that all of the three criteria occur in varying degrees and proportions in the different cases it seems desirable for one to have an evaluation of each of these three criteria in order to attempt a careful evaluation of a given case.

### SUMMARY

Eighty carefully selected cases of essential hypertension were studied from the point of view of retinal vascular changes and electrocardiographic alterations, and 59 of them as to radiological heart size, and a correlation between these criteria was carried out.

Retinal vascular changes were noted in all of the selected cases, with 88.8 per cent graded as sclerosis, hypertensive type. The electrocardiogram revealed final deflection changes in 68.8 per cent. A slight to moderate enlargement of the heart was noted in 50.8 per cent, and a marked degree in 27.1 per cent.

There is a trend towards a positive correlation between electrocardiographic alterations and the grade of the retinal arteriolar changes, between cardiac enlargement and the grade of the retinal arteriolar changes, and between electrocardiographic alterations and the degree of cardiac enlargement. This correlation was not demonstrated to be of high statistical significance.

Some of the possible causes for this incomplete correlation are discussed, among which the irregular distribution of the vascular processes and the lack of strict parallelism between the systemic and central retinal artery blood pressure are stressed.

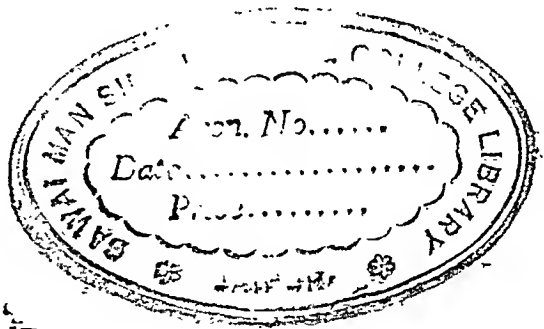
Inasmuch as there is an inadequate correlation between the three criteria in question, it seems desirable to have, in a given case of essential hypertension, an evaluation of the eyeground, electrocardiogram and heart size, in addition to the more routine studies, when one attempts the difficult task of making a practical prognosis for a patient who has this disease.

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# HYPOGLYCEMIA FOLLOWING ENCEPHALITIS \*

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THE recognition of hypoglycemia as the causative factor in the production of a fairly definite group of symptoms has commanded considerable attention in recent years. Both from experimental and clinical observations it has been associated with a wide distribution of pathological lesions. These are tabulated below.

## *Causes of hypoglycemia*

- I. New-born infants.
  - A. Starvation;
  - B. Diabetic mother.
- II. Pituitary.
  - A. Experimental ablation (uncontrolled insulin action);
  - B. Deficient anterior secretion (increased insulin action);
  - C. Pituitary pancreatropic substance;
  - D. Simmonds' disease;
  - E. Basophile adenoma;
  - F. Adiposogenital dystrophy.
- III. Thyroid.
  - A. Experimental ablation;
  - B. Myxedema;
  - C. Cretinism.
- IV. Adrenal.
  - A. Experimental ablation;
  - B. Addison's disease.
- V. Liver.
  - A. Experimental ablation;
  - B. Hepatic destruction—carcinoma, hepatitis, cirrhosis, eclampsia, yellow atrophy, hepatoxins.
- VI. Pancreas.
  - A. Islet hyperplasia;
  - B. Adenoma;
  - C. Adeno-carcinoma.
- VII. Spontaneous hypoglycemia. Spontaneous hyperinsulinism, cause unknown, comprises the majority of these cases.

At the present we are concerned only with group VII—spontaneous hypoglycemia. It is true that many cases that have been included in this group may have been due to one of the other causes, particularly lesions of the pancreas, which were not recognizable during life. It is also possible that

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one or more of the cases to be reported below may also be due to a definite anatomical lesion which up to the present has not been detectable.

Spontaneous hypoglycemia must result from some derangement of the equilibrium of carbohydrate metabolism. It is well known that this may occur from a variety of causes which cannot always be demonstrated upon an anatomical basis. The experiments of Claude Bernard demonstrating that puncture of the hypothalamic area would produce hyperglycemia are well known and have been amply corroborated by pathological lesions in this area. The relation of cerebral lesions to hypoglycemia has not, however, as yet received the attention that it may in future warrant.

Following are the case reports of three patients all of whom suffered from hypoglycemia, the clinical pattern of which followed shortly after what was presumed to be an attack of influenza, but in time these patients developed also a Parkinsonian syndrome of varying severity.

*Case 1.* A. R. C., a woman 24 years old, had had good health until February 2, 1931. For eight days she suffered from acute influenza and on February 27 had diplopia and headache.

On March 4, 11:30 a.m., there was sudden onset of sweating, trembling, syncope and loss of consciousness which lasted about an hour, during which convulsive movements were noted. On recovery from this she was very hungry and craved sweet biscuits. This was followed by a period of fatigue and lethargy. A similar attack with no loss of consciousness occurred at 5 p.m. and was relieved by tea and cake. These episodes continued intermittently, usually in late morning or afternoon, with loss of consciousness about every third one. They had been considered grand mal in character, but in late April tremors of the fingers when at rest were noticed by her family and during the next six months the classical features of Parkinsonism developed.

In October, I saw one of these attacks for the first time. She was unconscious, sweating and had generalized twitchings. Her pupils were unequal, the skeletal muscles rigid with indeterminate reflexes. The Babinski response was positive on one side. The blood pressure was low. Rapid recovery followed the giving of 25 c.c. of 10 per cent glucose intravenously. A later estimation of the blood sugar was 35 mg. per cent. The blood sugar curves of October 17 and 26 are illustrated in chart 1. On October 26 the basal metabolic rate was minus 4—plus 2. The plasma potassium was 19.8 mg., calcium 10.1 mg., non-protein nitrogen 28 mg. per cent. The skull roentgenogram, the fundi and the gastric acidity were normal. Systolic blood pressure 125, diastolic 85.

It was found that the ingestion of small amounts of carbohydrate at short intervals gave partial relief from attacks. Stramonium controlled the Parkinsonism to some extent but had no effect on the convulsions without proper diet. A nasal spray of epinephrin appeared to have some effect on the latter. In November it was decided to operate in the hope of finding a pancreatic adenoma. The pancreas appeared normal and about one-half of it was removed. This was followed by a slight temporary improvement. The blood sugar curves of November 10 and December 19 are given in chart 1.

During November and December, 1931, and January, 1932, minor attacks occurred which were controlled with glucose and epinephrin. Frequent small meals, high in fat, and sedatives constituted the routine treatment. On January 21, about 5 p.m., when the patient was unattended she apparently had a severe attack. Her afternoon tea

served at 4:55 was poured but remained untouched. It was her desire to be left alone at meals on account of her Parkinsonian disability. At 6:30 the maid found her unconscious. When help arrived she was dead. A partial autopsy consisting of the pancreas, spleen, liver, adrenals, thyroid and brain was obtained. All organs were essentially normal but the brain, which revealed the typical findings associated with postencephalitic paralysis agitans.

*Case 2.* This patient, a man, had a severe attack of influenza on December 23, 1932, which was followed by a slow convalescence. About the middle of January he had an attack characterized by a feeling of fullness in the head, violent trembling, profuse sweating and weakness in the legs. He was first seen by me on November 7, 1934. It was noticed that the right palpebral fissure was larger than the left, the right pupil twice the diameter of the left, there was tremor of the arms and legs and the hands were cold, clammy and cyanosed. Insomnia was most troublesome. His friends found that his facial expression had altered, having become mask-like and dour; and

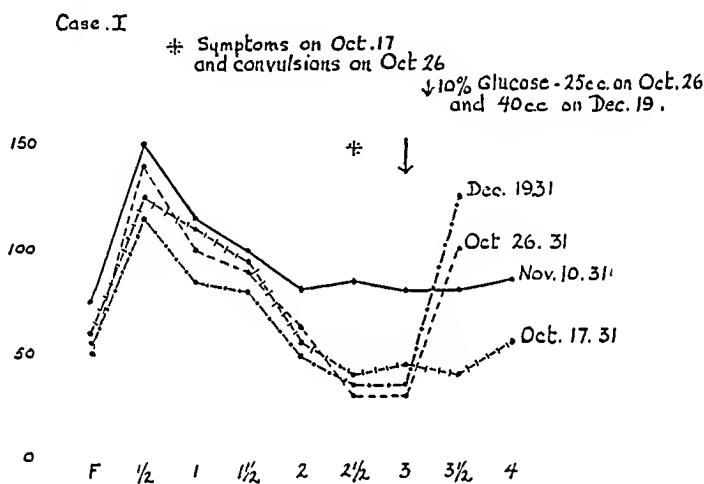


CHART 1. Four blood sugar curves of Case 1. The curves of October 14 and 26 were before operation, that of November 10 a week post-operative, and that of December seven weeks post-operative—practically identical with the pre-operative curves.

they claimed that his personality had changed, that he was irritable and secretive, had lost business ability and had decreased power of concentration. Sodium pentobarbital controlled the frequent attacks which occurred in the late morning, late afternoon and at night. Intravenous administration of glucose, 0.2 mg. per kilo of body weight, did not produce hypoglycemia. Attacks were relieved by sugar by mouth or by 0.75 c.c. of adrenalin.

The basal metabolic rate was  $+13$ . Examination of the urine, the blood count and chemistry, the spinal fluid and a skull roentgenogram revealed nothing abnormal. The blood sugar curve is shown in chart 2.

During 1935 the attacks continued, particularly towards noon. Reduction in the carbohydrates of his breakfast gave some relief, but increasing amounts of sodium pentobarbital and alcohol were taken. In December he had an unusual blood sugar curve (charts 2 and 3). He was given 4 c.c. of ergoklonin which produced a rapid fall. On January 1, 1936 he was given 4 c.c. of ergoklonin every six hours for four doses. The blood sugar curves were flat and low. This regimen was continued for some months and the attacks became fewer. During 1937 the attacks recurred at long intervals and were mild. The patient continued to take pentobarbital and alcohol.

The blood sugar curves are shown in charts 4 and 5. In November when attacks had been absent for six months he entered the hospital where the pentobarbital and alcohol habits were successfully treated. Until March 1940 there have been no further attacks.

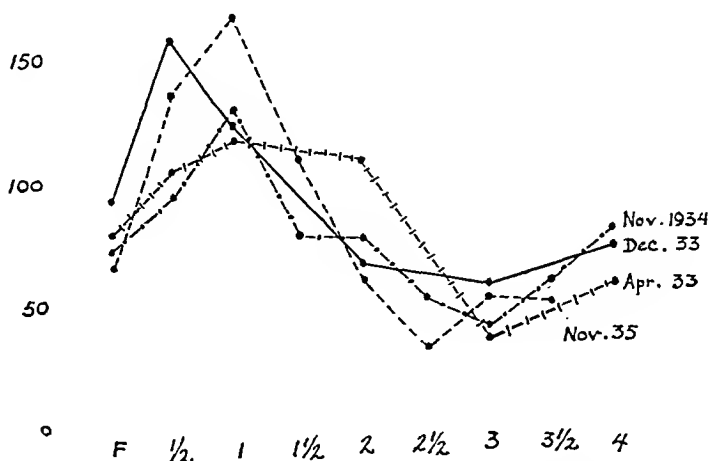


CHART 2. Blood sugar curves in Case 2, from April 1933 to November 1935, revealing a fairly consistent type of curve, with hypoglycemia between the two and half and three hours.

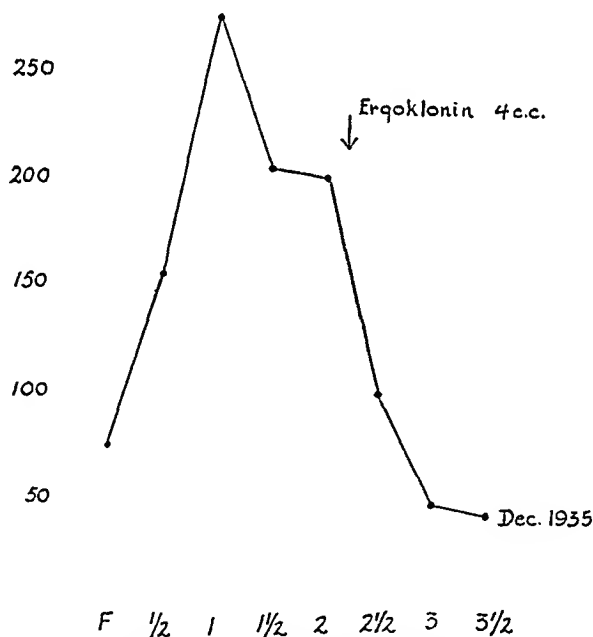


CHART 3. Blood sugar curve of Case 2 in December 1935. This was an unusual finding. Ergoklonin 4 c.c. was given which appeared to produce a sudden fall in blood sugar.

Case 3. In January 1932, a patient of Dr. Miller, Moose Jaw, Sask., had a severe attack of influenza which apparently lasted for three weeks although the patient himself does not think that he ever completely recovered. Dizzy spells preceded by occipital headaches made their appearance in May, accompanied by such weakness of the legs as to cause the patient to fall. These at first occurred about once a week,

but their frequency increased to five a week. The typical attack was always preceded by a headache which increased in severity during one and a half hours, leading to vertigo with objects rotating from right to left, ataxia and finally stupor. They were followed by weakness, trembling, sweating and irritability. Glucose or adrenalin would abort the attacks. From clerical work he turned to farming, and in the fall had his first attack of unconsciousness, which lasted one and a half hours. Another occurred a month later, both in the late afternoon.

In December he was admitted to the hospital. On physical examination he appeared normal except for tenderness in the right upper abdomen. Roentgenographic



CHART 4. Blood sugar curves on Case 2 during December 1935, and January 1936, the period when the patient was receiving ergoklonin. Note the irregularity and inconsistency of the curves.

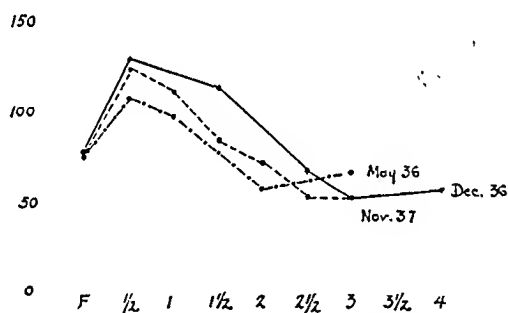


CHART 5. (Left) Blood sugar curves on Case 2 during 1936 and 1937. Note the similarity of the curves and the absence of gross hypoglycemia. The patient during this time was comparatively free of symptoms.

studies revealed a duodenal ulcer and pylorospasm. His blood pressure was systolic 114 and diastolic 72. The urine and blood examinations were negative. The basal metabolic rate was  $-4$ . The Wassermann reaction was negative and the fasting blood sugar was 42 mg. per cent. He was given a diet consisting of CHO, 100 gm., protein 60 gm., and fat 250 gm., with corn syrup and adrenalin to relieve attacks. This was followed by much improvement.

During January 1933 the high fat diet was not tolerated well; the patient refused meals and attacks became more frequent. The CHO was increased to 200 gm. and the fat reduced to 150 gm. The attacks continued but were relieved by concentrated

CHO hourly. The blood sugar curves during January and February are shown in chart 6.

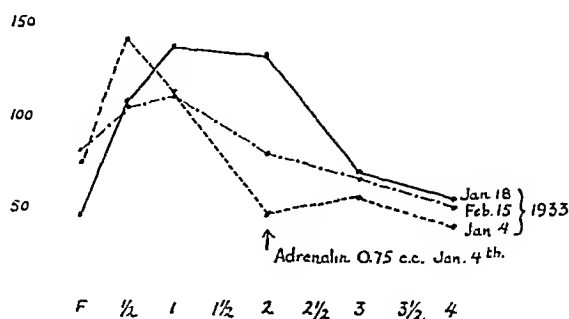


CHART 6. (Right) Blood sugar curves on Case 3 before operation.

On March 18 the possibility that a lesion of the pancreas might be present prompted abdominal exploration. No pancreatic tumor was found, but about two and a half inches of apparently normal pancreas were removed. The blood sugar curve of March 24 is shown in chart 7.

During April the attacks of dizziness returned, and on May 17 the patient had a late afternoon period of unconsciousness. A blood sugar curve of May 22 also appears in chart 7.

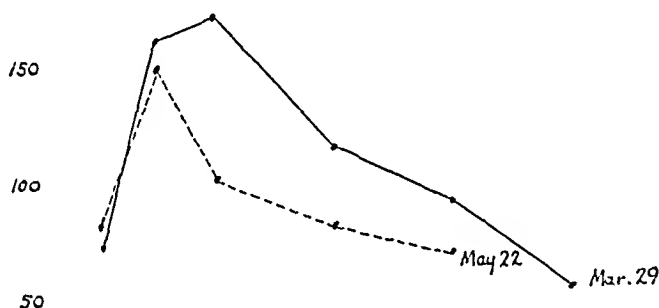


CHART 7. Blood sugar curves on Case 3 after operation. Note the temporary improvement in the curve of March 29, one week after operation, and compare with similar improvement revealed in the curve of Case 1, on November 10, chart 1.

Since 1933 there have been occasional attacks of unconsciousness. In 1936 he made an uneventful recovery following a broken arm. That fall he had hallucinations of obscure animals when he was in the dark. At present he shows absent-mindedness, inability to concentrate and irritability. He also has anorexia and abhors fats. The attacks are controlled with frequent CHO feedings.

These cases are reported in the hope that others of a similar nature may be detected. It is merely suggested that there is a connection between a possible hypothalamic lesion due to a post-influenzal encephalitis and the hypoglycemia. Certain experiments would tend to support this possibility. Miki (1932) found that hypoglycemia occurred following injury to the paraventricular nucleus in rabbits. D'Amour and Keller (1933) reported hypoglycemia in five out of 13 dogs following bilateral transverse lesions of the chiasmal end of the hypothalamus. Barris and Ingram (1935) also

produced hypoglycemia in 10 cats. The lesions were not always of constant distribution; in eight there was injury of the anterior hypothalamus, in two in the tuber region, in the posterior hypothalamus in two, and injury or atrophy of the nucleus filiformis in eight. They also noted that the hypoglycemia was often intermittent.

Clinical observations to substantiate these experimental findings are very rare. Adlersberg and Friedman (1934) reported upon the carbohydrate metabolism in post-encephalitic Parkinsonism in 21 cases. In only three did they find definite hypoglycemia following a hyperglycemia after the ingestion of 50 grams of glucose. The evidence, therefore, is still incomplete as to whether there is a true correlation between hypothalamic lesions and hypoglycemia, and further, if this should be so, whether the effect is operative through the pancreas, liver, or adrenal. To answer these questions will require more extensive experimental and clinical investigations. It seems quite likely that a spontaneous improvement may occur in these cases without extirpation of part of the pancreas.

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# THE PROBLEM OF RHEUMATISM AND ARTHRITIS

## REVIEW OF AMERICAN AND ENGLISH LITERATURE

### FOR 1938

(Sixth Rheumatism Review)\*

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## Part II

### CHRONIC ARTHRITIS: THE GREAT TYPES

*Clinical and Etiologic Relationships.* Only a few years ago the majority of students of this subject were content to write of "chronic arthritis," making little or no attempt at a finer distinction. But such an abundance of evidence has accumulated indicating unmistakable clinical, chemical, immunologic, pathologic and radiologic differences between the several forms of "chronic arthritis," particularly the atrophic and hypertrophic forms, that few indeed are the current writers who fail to make the distinction. One physician <sup>768</sup> reported 150 cases of chronic arthritis which he carefully classed into atrophic, hypertrophic and mixed forms, but in his subsequent detailed analysis he ignored the classification and grouped them all together "as it appears that fundamentally they are the same disease." This is unfortunate because it makes it almost impossible to consider such a report in relationship to other current studies. It is the privilege of any physician to believe (as some authorities <sup>763</sup> still do) that, despite certain striking differences, atrophic and hypertrophic arthritis have close basic relationships, but nowadays when such physicians wish to command the attention of serious students of the subject, they carefully preserve the now generally accepted amenities of classification, and discuss the clinical features of each group separately. This done they are at full liberty to call attention to the supposed common attributes of the different types. The fact that so few contributors to the literature under review stressed the relationship affords evidence that the trend of rheumatology is to make the distinction between the great types more and more, rather than less, definite.

#### ATROPHIC (RHEUMATOID, PROLIFERATIVE, INFECTIOUS) ARTHRITIS

*Relative Incidence.* Although atrophic arthritis is "the real scourge," it is responsible for less than 50 per cent of the cases classified as "rheumatism." <sup>63, 64</sup> There were only 1,842 cases of atrophic arthritis among 5,000 cases of "rheumatism" at the Institute of Ray Therapy, London. According to Beaumont many cases of "arthritis" in reality are due to fibrositis.

*Influence of Climate, Geography and Race on Incidence.* Many patients of Coste and Forestier were affected badly by sea climate, whether that of the Mediterranean, the cold windy English channel or the Atlantic Ocean. They felt worse in northern France and in the damp western French plains, better in warm dry sections away from the sea. Atmospheric dryness and low electrical potential, "which is especially low in towns," seemed more important factors than temperature. "It is not proved that polyarthritic patients feel worse in winter than in summer. Some of them bear great heat badly and have a severe attack in August," perhaps from the effects of atmospheric ionization. Hodge noted in India a juvenile form of rheumatoid arthritis which somewhat resembled acute rheumatic fever (high fever,

severe articular pain and swelling, tendency for slight relative mitral insufficiency to develop "from toxic myocarditis"), but the articular symptoms persisted unresponsive to salicylates, and true valvulitis did not develop.

*Sex and Age Incidence.* Of 343 patients seen by Thompson, Wyatt and Hicks 153 (45 per cent) were males, 190 (55 per cent) were females. [The usual sex incidence is about one male to two or three females affected.—Ed.] Among these same patients the disease began among both males and females at an average age of 37 years. The youngest patient was aged two, the oldest, 71 years. Although the greatest incidence is between the third and fourth decades of life, the disease may occur at any age.

*Effect of Difference of Constitution on Incidence.* The cases of Breuer bore no relationship to body weight or physical constitution.

#### GENERAL CLINICAL DATA: SYMPTOMS AND COURSE OF ATROPHIC ARTHRITIS

The well-known British classification<sup>219</sup> which divided atrophic (rheumatoid) arthritis into a "primary type" of unknown etiology and a "secondary type" caused (presumably) by infection was defended with scant enthusiasm by Edgecombe and Ellman<sup>281</sup> to whom the clinical, pathologic, biochemical and radiologic features of both seemed very similar, if not identical. Van Dam also saw no significant radiologic differences between "infective" and "rheumatoid" arthritis. But Stone regretted the confusion of "chronic infective arthritis" with "rheumatoid arthritis." More descriptive than "rheumatoid arthritis" was Charcot's old term "progressive symmetrical polyarthritis," a disease characterized by its predilection for young women, pyrexia of low grade, anemia, loss of weight, malaise, symmetrical involvement of joints (usually hands first) and roentgenograms which reveal generalized decalcification of bone not seen in "chronic infective arthritis." On the contrary chronic infective arthritis may not affect joints symmetrically, may not begin in hands and may long affect one large joint. Although they approved the clinical separation of these two supposed types, Copeman<sup>215</sup> and Stone admitted that both types "demand the same therapeutic measures and respond in much the same way."

[Fewer English writers than usual supported this distinction which is rarely accepted in the United States.—Ed.]

The prodromal symptoms of "the pre-arthritic stage" of the disease were reviewed.<sup>215</sup> Clinical details in 343 cases of atrophic arthritis were reported by Thompson, Wyatt and Hicks, in 50 cases by Breuer, and in 165 cases (involving shoulders) by Kulms. Blood pressures in Breuer's cases were "as one would find in a similarly sized group of persons selected at random." Thompson and his colleagues, being located at Tucson, a rheumatism resort, saw arthritic patients of the "last resorter" type; the average duration of their disease when they were seen was 6.5 years: deformities were already present in 60 per cent of the total, in 55 per cent of the females, in 45 per cent of the males.

■ Among 1765 patients with atrophic arthritis studied by Kuhns, shoulders were affected in only 165 (9 per cent). They were affected with equal frequency at all ages and in both sexes, but especially in (half of the) patients with atrophic (Strumpell-Marie) spondylitis. In atrophic arthritis when shoulders are affected, both are involved usually. Pathologic reactions therein are similar to those of other joints, but symptoms are greatly out of proportion to roentgenographic changes. There was rapid destruction in only three of Kuhn's cases, severe damage visible in roentgenograms in only eleven, ankylosis in six, unilateral subluxation in one. Muscle atrophy was common; tenderness, uncommon; palpable swelling, rare. "Marked swelling [of shoulder joints] is seen only in such conditions as tuberculosis or suppurative arthritis, never in chronic arthritis." [Bursitis sometimes produces marked swelling at shoulders.—Ed.] Extensive pathologic changes were commonly seen in acromioclavicular joints, but no ankylosis. Arthritis of shoulder joints tends to progress slowly, generally without the exacerbations which affect weight-bearing joints, and often almost painlessly, to a stage of marked limitation of motion unless early vigorous treatment is instituted.

Anomalies of the skin, sometimes seen in atrophic arthritis, were listed by Barber and Pringle as a cold clammy state simulating Raynaud's disease, pigmentary disturbances, psoriasis, lupus erythematosus, erythema induratum and subcutaneous nodules. The association of psoriasis with chronic arthritis will be discussed further under the heading "Psoriatic arthritis."

#### ATROPHIC ARTHRITIS: SPECIAL CLINICAL FEATURES

*Effect of Jaundice.* When patients with atrophic arthritis (or with primary fibrositis) become definitely jaundiced a notable event usually occurs: their rheumatic symptoms are rapidly, markedly and generally completely alleviated for some weeks or months. This phenomenon, casually mentioned by Still (1897) and by Wishart (1903), was discussed in detail by Hench (1933). Hench<sup>430, 432</sup> has reported further observations on the phenomenon as it appeared in 19 more cases of atrophic arthritis and in nine more cases of primary fibrositis. Observations also were made of four patients with atrophic arthritis and of nine patients with other types of articular and neuritic complaints who were *not* relieved of symptoms coincident with jaundice.

Symptomatic remissions lasting from 5 to 82 (average 18.5) weeks occurred in the 19 new cases of atrophic arthritis (average duration 5.5 years) in which intrahepatic or obstructive jaundice lasted an average of 9 weeks. Remissions of from 4 to 104 weeks occurred in nine cases of primary fibrositis in which the jaundice lasted an average of 5.6 weeks. (Two patients with lumbosacral and sciatic pain and one with secondary hypertrophic arthritis of hips had jaundice and symptomatic remissions; both jaundice and remissions lasted an average of five weeks.) The degree of relief obtained was complete in 12 (63 per cent) of the 19 cases of atrophic arthritis and in all of the nine cases of fibrositis; it was notable but incomplete in seven (37 per cent) of the arthritic cases. "Relief" implied notable or complete amelioration of symptoms of active disease. Articular pain, active articular swelling, muscular stiffness, soreness and fatigue were reduced markedly or disappeared. Residual articular thickening and stiffness from deformity were unaffected.

Jaundice developed in four cases more than once: mild jaundice did not produce remissions in rheumatic symptoms, but when jaundice was more intense the phe-

nomenon of relief was repeated with each attack of jaundice. No cumulative effect was noted; subsequent remissions were not necessarily longer than the first. When the phenomenon was invoked, it generally appeared promptly, often dramatically, usually within the first two or three days of visible jaundice, but occasionally even before jaundice was visible. The phenomenon was usually obvious to those affected and evoked such remarks as "When the jaundice came in the front door the rheumatism went out the back door." Spontaneous jaundice induced a remission, not a cure. The duration of remissions bore a general, but not a specific, relation to the intensity and duration of the jaundice. Remissions lasted from three weeks to several months; they averaged roughly from two to three times the average length of jaundice. Subsequently, rheumatic symptoms returned "as before" in 48 per cent of cases, less intensely in the rest.

In general the phenomenon was dependent more on the quantity than on the quality or "type" of jaundice. It was invoked by catarrhal, infectious, or spontaneous intrahepatic jaundice, by "cinchophen jaundice" and by obstructive jaundice from stones or malignancy. A mild jaundice was generally ineffective, the "zone of therapeutic effectiveness" seemed to begin at, and continue above, a level of about 8 mg. of bilirubin per 100 c.c. of serum. In four cases of atrophic arthritis with mild jaundice (serum bilirubin below 4 or 5 mg. per cent) relief was not noted. Inter-current jaundice of several types and degrees did not alleviate symptoms of nine patients with other painful conditions (acute gouty arthritis, "toxic" or infectious arthralgia, juxta-articular malignancy, ischemic neuritis, postherpetic neuralgia). Therefore the phenomenon appears (so far) to be relatively specific for atrophic arthritis and primary fibrositis.

Conclusions of Hench were as follows: 1. Atrophic arthritis (and fibrositis) can no longer be regarded as necessarily relentless, uncontrollable diseases for which no rapid method of control should ever be expected. Although certain pathologic changes may be permanent, the pathologic physiology of these diseases is more rapidly reversible than previously supposed. 2. Regardless of the supposed validity of the infectious theory, atrophic arthritis and fibrositis can be affected profoundly by a phenomenon primarily chemical. 3. Nature possesses a highly effective method of producing dramatic remissions involving a phenomenon which is precipitated more rapidly by jaundice than by any other physiologic or therapeutic method.

This phenomenon was also noted by Thompson and Wyatt<sup>950</sup> in two cases.

One patient with atrophic arthritis had jaundice from neocinchophen (serum bilirubin 24 mg. per cent) which lasted 30 days, during which time "articular symptoms were entirely relieved." In another case, that of a child with severe polyarthritis, severe jaundice developed after a transfusion. Jaundice was intense (serum bilirubin 12 mg. per 100 c.c.) but lasted only five days; nevertheless "with the onset of jaundice the swelling and pain diminished, the arthritis completely disappeared and the child remained well for 16 months, after which symptoms returned with less severity."

Attempts which have been made to reproduce the phenomenon as a form of experimental therapy for atrophic arthritis will be discussed under treatment.

Hartfall, Garland, and Goldie<sup>5</sup> noted no ameliorating effect from the jaundice induced by gold salts. [The concentrations of serum bilirubin were not reported in these cases, but in at least 13 of the 85 cases of "gold jaundice" the

jaundice was "severe."—Ed.] But Burt <sup>145</sup> noted the "temporary cure" of a patient taken ill with jaundice after gold injections.

[The mechanism whereby jaundice operates to invoke this phenomenon can be determined only by noting what types and degrees of jaundice produce it and what types do not. Hence further observations on the effects on atrophic arthritis of jaundice related to chrysotherapy seem important.—Ed.]

The ameliorating effect of jaundice in two cases of sciatic pain (associated with fibrositis in one case, with pelvic malignancy in the other) was reported by Hench (1933). Lichtman, extending this observation, reported an interesting association among sciatic neuritis, hepatic disease and jaundice in five cases.

*Case 1.* The patient had had indigestion for many years before "sciatica" developed. After the latter had lasted six months jaundice developed spontaneously. [The concentration of serum bilirubin was not given.] "With the onset of jaundice" the pain in the left lower extremity became milder but did not disappear. At death, subacute liver atrophy was found.

*Case 2.* The patient had had salvarsan for syphilis and five years later severe sciatica. Spontaneous "catarrhal jaundice" developed three weeks after the sciatica. "The sciatic pain subsided with the onset of the jaundice," and had not recurred four years later.

*Case 3.* A patient at the age of 26 years had paratyphoid fever, and a year later severe sciatica. Enlargement of spleen and liver were noted respectively two and four years after the fever. When he was aged 43 years sciatica returned and continued intermittently for two years. Then nausea, fever and jaundice developed, and "the sciatic pain subsided." When the jaundice subsided the sciatic pain recurred.

*Case 4.* A patient had severe sciatic pain unrelieved by various measures. Twelve weeks later 5 grains of cinchophen were taken but were not regarded as responsible for the anorexia, epigastric distress and jaundice which developed one week later. "The sciatic pain definitely subsided with the onset of jaundice." At death subacute liver atrophy and pancreatitis were noted.

*Case 5.* This patient had sciatica with "excruciating pain." The icterus index of blood was 15; the bilirubin content was 0.6 mg. ("slightly elevated"). Two weeks later they were 8 and 0.3 mg. respectively ("normal"). "The decrease in the latent jaundice occurred simultaneously with the subsidence of pain."

Commenting on these cases Lichtman stated that the relief from pain attributable to the analgesic effect of jaundice "was greater than could be expected from confinement to bed alone." He therefore tested the analgesic effect of bile salts by introducing them into the spinal canal of cats: no analgesia was produced. He suggested that endogenous toxic substances, responsible for the peripheral sciatic neuritis, may also be responsible for hepatic injury.

[The observations of Hench and Lichtman on the ameliorating effect of jaundice in two such dissimilar conditions as atrophic arthritis and sciatica suggest that the effect is nonspecific in character.—Ed.]

*Influence of Pregnancy.* During the last century many physicians have believed that chronic arthritis is related etiologically to defective catamenia, other uterine disorders, the menopause, too rapid childbearing or prolonged

lactation, and that pregnancy is dangerous for women with arthritis because disease of the joints is likely to flare up after parturition.<sup>431</sup> The latter point is illustrated in the case of De Sa.

Eight months after completing her first pregnancy a woman developed severe progressive "arthritis deformans" of hands and feet, unrelieved by therapy. Three years after birth of her first child she conceived again: "During this pregnancy she suffered now and again from pains in fingers and toes." A month after the second confinement an acute exacerbation of polyarthritis developed which eventually necessitated tenotomies and amputation of deformed toes so that she could walk. Even so she was crippled badly. The patient was later (time unstated) seen by De Sa in the second month of her third pregnancy. Suspecting that some latent pelvic or other focus of infection was somehow activated by pregnancy and fearful of another post-partum exacerbation, De Sa terminated the pregnancy by hysterectomy.

[It should be noted that both the primary arthritic attack and the subsequent exacerbation came respectively 8 months and 1 month *after* parturition, not during pregnancy.—Ed.]

Hench studied the effect of 37 pregnancies on 22 women with chronic articular disease and concluded that, regardless of the aftermath, pregnancy, like jaundice, initiates a physiologic state which is decidedly beneficial (at least temporarily) to patients with certain articular diseases, notably atrophic arthritis.

Fifteen of the patients had atrophic arthritis, one had atrophic arthritis with recurring symptomatic hydrarthrosis; one had true (idiopathic) intermittent hydrarthrosis independent of later atrophic arthritis in other joints; one had localized lumbar arthritis, presumably infectious; two had psoriatic arthritis and two had periarticular fibrositis. Twenty of the 22 patients obtained marked, generally complete relief of articular symptoms during pregnancy and for variable periods thereafter. These 20 patients had 34 pregnancies, in 33 of which the phenomenon of relief appeared; the phenomenon did not appear in a case of early tubal pregnancy. Thirteen patients experienced the phenomenon in one pregnancy; three noted it with each of two pregnancies, two noted it three times, one noted it four times, and one noted it in each of her four intra-uterine, but not in her (fifth) tubal pregnancy. Articular relief began generally (in 16 instances) about the fourth week of pregnancy, occasionally not until the sixth week or the fifth month of pregnancy. Pain, swelling and stiffness were relieved markedly (during 13 pregnancies) or completely (during 19 pregnancies). The relief was obvious to the patients: one stated, "There's no relief like pregnancy"; another decided she "ought to keep pregnant all the time." Three patients deliberately became pregnant to enjoy the relief which one had experienced during a previous pregnancy and which two had heard of. The symptomatic remissions induced by pregnancy generally ended about four to eight weeks after parturition, occasionally considerably later. The average duration of relief was 9.4 months (shortest 5, longest 30 months). Return of articular symptoms bore an inconstant relationship to post-partum lactation and restoration of menstruation. After parturition the disease returned "as before" in eight cases, slowly and progressively in five, precipitously in four. In one case the disease was progressively less severe after each of four pregnancies.

Two women with moderately severe atrophic arthritis were apparently unrelieved by one and two pregnancies respectively: one of these, unrelieved by two pregnancies, also had noted no articular relief during a previous attack of jaundice (of unknown intensity).

[Several casual references have previously appeared<sup>431</sup> concerning the beneficial effects of pregnancy on intermittent hydrarthrosis, and also on atrophic arthritis. Passing comments on the latter were made by Garrod (1890), Strangeways (1907), Pemberton (1920), Llewellyn (1927), and Murphy (1936). Perhaps the most interesting comment of all appeared recently in "Queries and Minor Notes."<sup>785</sup> An anonymous physician commented thus: "A woman, aged 38, with polyarticular arthritis for the past 10 or 12 years, is entirely free from symptoms during pregnancy. She had nine pregnancies with return of the trouble between the termination of each labor and the next pregnancy. There is a definite aggravation of symptoms during the menstrual period."—Ed.]

It seemed logical to Hench to believe that the agents responsible for both of these phenomena (relief from pregnancy or from jaundice) are closely related, probably identical, and if the agent is a chemical substance, it is probably neither bilirubin (which does not rise appreciably in pregnancy) nor a strictly female sex hormone (since jaundice relieved male arthritics). Such diverse substances as cholesterol (which increases in the blood during pregnancy), ergosterol (the precursor of vitamin D), some of the sex hormones, cortin, and bile acids are closely related: they all contain the phenanthrene nucleus. "If the potent common denominator of these two phenomena can be discovered, progress in treatment may be expected."

Touw and Kuipers also saw three patients whose articular symptoms were relieved markedly during pregnancy.

*Case 1.* A woman, aged 34 years, had had progressive "primary chronic polyarthritis" for 14 years. She had borne five children: "During her pregnancies she did not know what rheumatism was." When seen later she had markedly active polyarthritis again.

*Case 2.* A woman, aged 37 years, had had "primary chronic polyarthritis" for seven years, with incomplete relief under treatment by solganol. Three years after this treatment she was seen in the fifth month of pregnancy "entirely free from complaints," but articular symptoms returned within six weeks after parturition.

*Case 3.* A woman, aged 26 years, had progressive bilateral stiffening of hips ("secondary arthrosis deformans" from old developmental epiphysitis); pain was worse before menses. After marriage she suddenly noticed that walking and cycling had become easier and practically painless. She could not account for this until a few weeks later she understood that she was pregnant. "Throughout the pregnancy the complaints had ceased. About four weeks after confinement, however, they returned, and have not left her to date."

Because of these observations Touw and Kuipers administered progestin with apparently successful results in two of the three cases.

[Another of us, M. H. D., has also studied the relationship between pregnancy and atrophic arthritis in 20 cases. As a rule the patients were considerably relieved of their arthritis during pregnancy, especially during the third trimester. Usually the arthritis became worse after delivery. However, in some cases the arthritis was apparently worse during pregnancy. In order to explain these phenomena various factors must be considered: the change in the patient's physical activities, the psychologic effect of pregnancy on the patient, and so forth. But it seems certain that pregnancy does exert a true physiologic effect in some cases of atrophic arthritis, and it is well-known that pregnancy exerts an inhibitory effect on certain other chronic diseases, notably tuberculosis, syphilis and psoriasis. Since this is true and since one of us, P. S. H., noted the inhibitory effect of pregnancy not only in atrophic arthritis but in fibrositis and intermittent hydrarthrosis, the effect of pregnancy would

appear to be nonspecific. Its relatively nonspecific nature makes the phenomenon seem less interesting to some physicians, less "tangible" and less important as a study for research than if it were specific for atrophic arthritis. But to other physicians the fact that the phenomenon may be relatively nonspecific makes a search for its cause all the more attractive. Perhaps, by studying the mechanism whereby pregnancy inhibits these diseases some therapeutic procedure of wide applicability may be discovered.—Ed.]

*Effects of Starvation and Anesthesia.* Occasionally one will read the casual statement that a patient with atrophic arthritis noted marked, if temporary, relief after anesthesia or some regimen involving complete starvation or semistarvation. Partial relief from the low caloric, low carbohydrate diet of Pemberton has been frequently commented on. One of us (P. S. H.) has seen a few arthritic patients who claimed to have received rapid and complete, but short-lived, relief after undergoing a few days of complete starvation at a western "Health School," and in one case he reproduced the phenomenon briefly. Thompson, Wyatt and Hicks observed remarkable reduction in the doughy swellings of atrophic arthritis after starvation, nausea, vomiting, diarrhea, and ether anesthesia. Except for the studies of Pemberton and of Pemberton and Scull<sup>3</sup> on low caloric regimens, these phenomena have received little or no scientific study.

[The effect of starvation (as contrasted to semistarvation) and of anesthetic agents should be examined further.—Ed.]

*"Opera-Glass Hand."* A rare deformity in chronic rheumatic disease is "la main en lorgnette" (Marie and Leri, 1913) or "opera-glass hand." In this condition, during severe and chronic polyarthritis absorption of phalangeal bone occurs to such an extent that telescoping of fingers results, with the appearance of transverse folds in the excess skin of the fingers, giving a paw-like appearance to the hand. The case of Marie and Leri affected a female, aged 70 years; that of Weigeldt (1929) affected a female aged 64 years. Nelson has reported another case, that of a woman, aged 31 years, who had had chronic severe polyarthritis (historically and objectively like atrophic arthritis) for 19 years.

Many joints were affected, some of the phalangeal joints were ankylosed, others were abnormally mobile because of the destruction of bone. The ulna had been dissolved so that it tapered to a long thin core. A large renal calculus and chronic purulent pyelonephritis for which partial nephrectomy was done developed. Much later, values for serum calcium, phosphorus and phosphatase were normal; "the test for rheumatoid arthritis was positive in agglutination of specific hemolytic streptococci in dilution of 1 to 1200." After death by terminal bronchopneumonia a parathyroid adenoma was discovered. Several bones were examined but were normal, as were the other glands of the body. Speculations were made as to the possible relationship of the adenoma to the bony condition.

[Gutman, Swenson and Parsons (1934) noted absorption of terminal phalanges in a case of proved hyperparathyroidism. Marked destruction and tapering of phalangeal bones as illustrated in Nelson's photographs have also been noted in cases of severe psoriatic arthritis.<sup>4</sup>—Ed.]



*Scleromalacia Perforans with Atrophic Arthritis.* Since the description of Van der Hoeve (1930), about 14 cases of scleromalacia perforans (scleritis necroticans) have been reported; 10 were associated with atrophic arthritis. Verhoeff and King have reported another case; the eye was examined microscopically.

A man, aged 52 years, had had progressive atrophic arthritis for 15 years. On the sclera of one eye five smooth waxy nodules appeared which were covered by conjunctiva, immovable, firm and tender. The eye was removed because of chronic pain unrelieved by narcotics. In the scleral abscesses the following had occurred: necrosis, a surrounding wall of epithelioid cells, penetration of the wall by pus cells with infiltration of the necrotic area, then slow formation of abscess and destructive edema.

*Association with Diabetes and Insulin Resistance.* The combination of atrophic arthritis and severe diabetes is unusual (Pemberton, 1935). Marble saw a woman, aged 35 years, with atrophic arthritis (for nine years) lymphadenopathy, slight hepatomegaly, and severe diabetes which was resistant to insulin and required 240 to 675 units of insulin daily. Eosinophilia (up to 33 per cent) regarded as "an allergic response provoked by the extremely large doses of insulin" was also present. The diabetes was controlled by a single morning dose of 150 units of insulin plus 220 units of protamine-zinc insulin.

*The Swollen Atrophic Hand.* A condition superficially resembling atrophic arthritis confined to one hand was described by Oppenheimer and will be discussed later (under "symptoms caused by narrowed intervertebral foramina").

#### PATHOLOGIC CHARACTERISTICS OF ATROPHIC ARTHRITIS

The pathologic reactions were described again in detail by Fisher and by Ghormley.

*Synovial Membrane.* The focal collections of round cells so frequently seen in synovial membranes in atrophic arthritis are considered by Ghormley to be nonperivascular and specific for this disease, by Fisher to be mainly perivascular and nonspecific. Inge's view was that many types of synovial inflammation produce the same basic pathologic reactions: synovial hypertrophy and hyperplasia with formation of villi and redundant folds, thickening of subsynovial layers by edema, fibrous engorgement of blood vessels and scattered foci of round cell infiltration. Any of these features may predominate in a given joint but "all are usually present in every case and with remarkable similarity" in cases of atrophic arthritis, infectious synovitis, or chronic trauma, "even in cases of osteoarthritis and of synovial osteochondromatosis." According to Inge the round cell infiltration is usually perivascular.

Jordan also doubted that the reactions of "rheumatoid synovitis" were specific. The injection of xylene or turpentine into the joints of rabbits produced synovial lesions, including round cell collections "practically in-

distinguishable" from those of human atrophic arthritis. In six cases of the latter he found that synovial changes varied with the degree and duration of the inflammation, and the microscopic picture may vary greatly in different sections taken from the same region of the same joint. Reactions in a case of only 2.5 months' duration were studied: no agglomerations of cells were seen. In older cases they were present and were apparently perivascular.

[Some of us do not believe the synovial reactions in atrophic arthritis are "specific" for that disease.—Ed.]

*Muscles; Bones.* In some cases wasting of bone and muscles may antedate considerably any evidence of intra-articular disease.<sup>539</sup>

*Nodules.* As noted under "Rheumatic Fever" Findlay, Hawthorne, and McEwen currently regard the nodules of atrophic arthritis as identical with or "very similar" to those of rheumatic fever. But Collins and Keil described certain differences. Special note should be made of the monographic report of Keil in which he reviews in great detail the similarities and differences between the subcutaneous reactions in rheumatic fever, Still's disease, gout, atrophic arthritis, fibrositis, panniculitis, periarteritis nodosa, and syphilis. The report (120 pages, 324 references) cannot be reviewed here.

#### LABORATORY DATA IN ATROPHIC ARTHRITIS

*Roentgenograms.* The roentgenographic features were reviewed.<sup>154</sup> Van Dam cited Huber (1896) as the pioneer radiologic student of arthritis. The amount of time which elapses between the onset of clinical symptoms and the earliest radiologic changes is never more than one year, according to Vesin and Volicer (1932); it may be many years according to Van Dam who stated that one of the earliest signs of the disease is a transverse contracture of the palm. This can be easily recognized by the projection of the metacarpal heads in roentgenograms: "the dorsal contour of the heads of the ulnar metacarpals moves in an ulnar direction in regard to the palm; the ulnar projections can also be seen to shift towards each other." These changes were illustrated in photographs and diagrams.

*Hemoglobin and Cell Counts.* The hemoglobin was "below 90 per cent" in most of Breuer's cases. There was no relation between the degree of anemia and the duration of the disease.

The total number of leukocytes was usually normal in Breuer's cases, often elevated in Collins' cases. Total number of leukocytes in Kahlmeter's 211 "stationary cases" averaged 6,681, in his 73 active cases 6,674; differential counts in the two groups were surprisingly alike, the only difference being a somewhat larger number of rod-nuclear neutrophils (6.2 per cent) in active cases than in stationary cases (4.7 per cent). The fact that the leukocyte counts remain normal whether the case is progressive or stationary and whether sedimentation rates are raised or not does not support the in-

fectious theory. In Gibson's cases<sup>357</sup> of atrophic arthritis (and of ankylosing spondylitis) the mean percentage of neutrophils was significantly greater than normal, that of lymphocytes was less than normal. Arneth counts were variable, normal counts being seen in some of Gibson's worst cases of atrophic arthritis. In general there was a significant shift to the left in atrophic, and also in hypertrophic, arthritis. (In fibrositis, and ankylosing spondylitis Arneth counts were essentially normal.)

Gibson divided cases of atrophic arthritis into two ill-defined groups according to their white cell picture. The lymphoid type with neutropenia of variable degree is associated with a shift to the left; the extreme example of this type is seen in so-called Felty's syndrome, as in the cases of Collins<sup>5</sup> in which the white cell picture simulated agranulocytosis. These findings are consistent with infection. The second type is more difficult to explain; although the patients are anemic, emaciated and toxic, they show a polymorphonuclear preponderance with a shift to the right in Arneth counts. Toxins, if present, appear to attack lymphocytes while the polymorphonuclears grow old and relatively numerous. These findings are unlike those in any infective process. "It is difficult to see that the leukocyte picture in rheumatism taken as a whole gives evidence either for or against an infective etiology."

There was no consistent correlation between Arneth counts and sedimentation rates<sup>201, 357</sup>; the two tests measure different abnormalities, the former cannot be used as a satisfactory index of improvement. Single or multiple applications of any one of several forms of physical therapy produced a drop in total leukocytes, especially polymorphonuclears, but no significant change in Arneth counts (Collins).

*Sedimentation Rates.* Rates were elevated in only 48 per cent of Breuer's cases, a smaller percentage than usual. [This suggests that not all of his cases were of active atrophic arthritis.—Ed.] Kahlmeter discussed biologic reactions involved in sedimentation rates. Normal rates (under 10 mm., one hour) were noted in 8 per cent of his 73 cases of active arthritis, and in 11 per cent of his 211 stationary cases (Westergren method). In these two groups respectively, rates were between 11 and 20 mm. in 10 and 12 per cent, between 21 and 40 mm. in 19 and 25 per cent, between 41 and 70 mm. in 38 and 36 per cent, more than 70 mm. in 25 and 16 per cent. Rates were not altered materially by single or multiple (over 5 or 6 weeks) applications of several forms of physical therapy.<sup>201</sup> Sedimentation tests afford the most useful index of prognosis and results of treatment. Shackle cited Orme to the effect that in cases of atrophic arthritis with rates over 50 mm. in one hour or 85 mm. in two hours the prognosis is relatively bad, improvement being at best very slow. In some severe cases rates periodically improve in summer, become more rapid in winter.<sup>854</sup>

Although the Westergren method is most commonly used, there are 17 or more different technics in current use; it is often difficult to obtain comparable values when a patient is tested by different methods. Because the test is so valuable in rheumatic cases Gibson considered it essential to insure its accuracy "so that it may be a method for precise quantitative measurement and not, as at present, a more or less vague qualitative test." Comparing various methods he concluded that the best technic in-

volved (1) use of oxalated blood with minimal or no dilution, (2) use of a tube at least 3.5 mm. in diameter ("the diameter of the tube clearly influences the rate"), (3) correction for red cell volume ("there is too great a tendency to shirk the need for this correction"). But Shackle stated that the bore of the tube used did not appreciably affect the results, and Bouton condemned the correction of rates for anemia or cell volume in rheumatic cases as "pseudo accuracy." The rate is "a nonspecific biological phenomenon with only approximate values." Hynes and Whitby described methods of correcting rates for anemia by means of hematocrit readings. A simplified method for such correction was described by Hambleton and Christianson. But the latter concluded that such a correction may introduce more errors than it eliminates, especially in cases with low cell volumes. Correction is valuable only when the cell volume is above 45 per cent, especially when the rate is relatively low. In cases with normal or subnormal cell volume "correction for cell volume is in general uncalled for." According to Shackle the most important source of error is failure to ensure exact verticality of the tube: "An inclination of two degrees out of the vertical is sufficient to double the rate, and three degrees to treble it."

The superiority of the differential serum vanadate sedimentation reaction as applied by Coke<sup>5</sup> to rheumatic cases was stressed by Hunt and Woodhouse. The discovery of a boy whose blood contained no fibrinogen made possible a study of the rôle fibrinogen plays in erythrocyte sedimentation. The boy's blood gave almost negligible sedimentation rates after one and two hours: hence fibrinogen plays a large, perhaps the largest, part in determining sedimentation.

*Blood Chemistry.* Freund discussed biochemical investigations in studies on rheumatic diseases. Despite the bone atrophy of this disease, estimations of serum calcium were "monotonously normal." Values for inorganic phosphates, phosphatase, uric acid, and cholesterol were generally normal. Distinctive glucose tolerance curves were noted by Shackle: (a sharp rise to abnormal heights but a sharp return to normal, usually without delay, and generally no glycosuria), they resembled those seen in exophthalmic goiter more than those in diabetes.

*Formol-Gel Test.* This test, as applied by Gibson and Richardson to chronic rheumatic patients, is a quantitative variant of the formol-gel test or aldehyde reaction of kala-azar. The test measures the rate of solidification of gelation and the degree of opacity which occurs in blood plasma to which a formalin solution has been added. It is not specific for rheumatism. [The reaction is increased in any disease with an elevated globulin.—Ed.] However, considerable but incomplete correlation between results of this test and sedimentation rates was noted. The test gave positive results in only 5 per cent of rheumatic cases with normal sedimentation rates, in 54 per cent of those with moderately rapid rates, in 97 per cent of those with very rapid rates. The correlation was notable in cases of atrophic arthritis, but in gout there was a dissociation between the results of the sedimentation and the formol-gel tests. Because of the dissociation apparent in those and other cases the formol-gel test cannot be used as a substitute for sedimentation tests, but it may be a distinctive index of rheumatic activity.

*Cytology and Chemistry of Synovial Fluid.* Data on the cytology and chemistry of synovial fluid in five cases of atrophic arthritis were reported by Jordan: total cell counts were 4,000 to 8,400; differential cell counts revealed

61 to 76 per cent polymorphonuclears, 22 per cent lymphocytes; value for dextrose was 17 to 76 mg. per cent (lower than the blood sugar); concentration of total protein was 4.12 to 6.65 gm. per cent, of uric acid 1.7 to 4.1 mg. per cent; of phosphates 4.0 to 4.3.

### ETIOLOGY AND PATHOGENESIS OF ATROPHIC ARTHRITIS

*Factor of Infection.* Recent work emphasizing the rôle of infection was reviewed by Gibson<sup>358</sup> and by Hensch.<sup>433</sup> The latter summarized all the arguments which have been made for and against the microbic theory, and also outlined the rebuttal used by the proponents and antagonists of the theory. The argument favoring the theory rests on 21 points, each of which is, for reasons given, discounted by the opponents of the theory.

1. Foci. In current literature the relationship between infected foci and atrophic arthritis was not made more clear. Although infected foci were found in 58 per cent of the 343 cases of Thompson, Wyatt and Hicks, none were found in 42 per cent. Of those with foci the following sites were considered infected: throat or pharynx in 23 per cent, sinuses in 19 per cent, gingival tissues in 13 per cent, tonsils or remnants, teeth or urinary tract in 10 per cent of each, lower part of respiratory tract in 5.7 per cent, female pelvis in 4.5 per cent, prostate in 4 per cent, gall-bladder in 1.5 per cent and colon in 1 per cent. [This adds up to 101.7 per cent. Some patients had more than one focus.—Ed.] Because injections of Paul's cutivaccine so often produced focal reactions (bleeding gums, loosening of teeth, tender roots) in radiologically normal teeth of patients with "chronic arthritis" Cmunt considered dental infection a common cause of the disease. In McCollom's 110 cases sinuses were not abnormal historically, radiographically and clinically in 63 per cent, were "positive" radiographically but "negative" historically and clinically in 26 per cent, definitely infected in 11 per cent. Coleman and Capps noted 30 cases of diverticulosis of colon; in 11 atrophic arthritis was a major complication. Except for two cases (one of prostatitis, one of cholecystitis) no other infection was found. Hemolytic streptococci were found in the colon in 9 of the 11 arthritic cases, in the throat in none. Because stools became normal and arthritic symptoms subsided under intestinal treatment the arthritis was considered related to the diverticulitis.

[The articular lesions were not described, simply diagnosed "rheumatoid arthritis." The fact that they subsided when diverticulitis improved would be sufficient for some critics to believe that the cases were *not* of ordinary rheumatoid or atrophic arthritis. Modern bacteriology also requires that hemolytic streptococci be grouped according to the Lancefield technic before any conclusions can be drawn.—Ed.]

Most cases of "chronic infective arthritis" are due to cervicitis, according to Robinson and Robinson who stated that chronic cervicitis is 15 to 20 per cent more common among arthritic, than normal, women, and may be present as a deep-seated infection even though the cervix looks normal. The

precursor of infective arthritis was said to be a "cervicitis syndrome" (malaise, vaginal discharge, low lumbar backache, fatigue). Oldershaw expressed similar views.

The changing views of one authority on arthritis were reported by Cecil and his colleague, Angevine. In 1927 Cecil and Archer noted 200 cases of "chronic infectious arthritis" (some of which might not be so diagnosed now). Infected tonsils were present in 61 per cent, infected teeth in 33 per cent, other infected foci in 15 per cent. Thus most of the patients had one or more infected foci, and many were definitely improved when foci were removed early. Hence foci of infection seemed to play a major rôle in the etiology of the disease. But today the situation is different; foci have been so energetically removed that one might exclaim, "Where are the foci of yesterday!" Of 200 consecutive new patients with "typical rheumatoid arthritis" 70 per cent had no demonstrable foci, 10 per cent had doubtful foci; only 20 per cent had definite foci (tonsils of 27, sinuses of 11, teeth of 2). Only a few patients were improved by removal of infected foci.

To evaluate the rôle of infected foci Cecil and Angevine attempted to create various infected foci in rabbits, by using a strain of hemolytic streptococci which on *intravenous* injection had produced arthritis in about 85 per cent of animals. Arthritis was produced in only 11 of 100 rabbits when other methods than the intravenous injections were used, and large doses had to be given to a most susceptible type of animal. Arthritis developed only in those animals from which streptococci were recovered shortly after injection. For these reasons Cecil and Angevine concluded: "The time has arrived for a complete revaluation of the focal infection theory. Undoubtedly there are cases of infectious arthritis which result from focal infection. However, as far as typical rheumatoid arthritis is concerned, it would appear that chronic focal infection plays a comparatively unimportant rôle." In his Billing's Lecture on "Focal infection: quarter century survey" Bierring took a less positive stand. He approved "the more conservative attitude [which] has developed with reference to hasty diagnostic conclusions and radical removal of suspected foci of infection." "It is the patient with a focal infection who requires treatment and not the focal infection alone." But he considered that clinical and bacteriologic evidence had afforded definite confirmation of the fundamental concept of focal infection and "perchance the 'Rosenow heresy' may yet become the medical guide of the future."

2. Joint cultures. These were negative by ordinary culture methods in the five cases of Jordan.

3. Agglutination tests. In 21 of Goldie's 28 cases agglutination of hemolytic streptococci at a titer of 1 in 200 occurred; in only 1 of 20 control cases was such agglutination exhibited. In 51 per cent of Levinthal's 119 cases similar agglutination tests on blood gave strongly positive results; they were weakly positive in 20 per cent, negative in 29 per cent. Similar tests made with synovial fluid rather than serum, indicated positive reactions

in 72 per cent, negative reactions in 28 per cent. But "out of 11 serum-negative cases not less than 8 showed positive reactions in the joint fluids." Apparently there are more antibodies in tissue cells than in the circulation. This led Levinthal to espouse the idea of a nonspecific bacterial allergy as the cause of the disease.

4. Precipitation tests. In Levinthal's cases this test with hemolytic streptococci almost always gave the same results as agglutination tests.

5. Antistreptolysins. These are less often present in cases of atrophic arthritis than in rheumatic fever. Goldie noted over 200 Todd units in 15 of 60 cases of arthritis, in only 1 of 50 control cases. Antistreptolysin titers above 120 units were found in 31 (78 per cent) of the 40 cases of Koerner and Poulton. This is a higher proportion than that reported by previous workers. The titer tended to fall in chronic cases.

6. Skin tests. Goldie made repeated skin tests with extracts of hemolytic streptococci in 85 cases; results of tests were positive at some time or another in 73 per cent. They were usually positive in old burnt-out cases, usually negative in severe cases of short duration; in the latter, reactions often later became positive.

*Theory of Bacterial Allergy.* This theory was acceptable to some<sup>570, 037</sup> but not to Aschoff who stated that the "allergic phase plays no part either in osteoarthritis, or in rheumatoid diseases arising from specific or non-specific infections."

*Virus Theory.* Virus-like bodies obtained from exudates of patients with atrophic arthritis were injected into monkeys: no lesions resembling atrophic arthritis resulted (Eagles, Evans, Keith and Fisher).

*Factor of Circulatory Disturbance.* Observations on nail-bed capillaries of 48 normal persons, 89 patients with atrophic, and 35 with hypertrophic arthritis were made by Pemberton and Scull. Various abnormalities of capillary flow were noted much more frequently among the arthritics (especially those with atrophic arthritis) than among the normals, and were often influenced favorably by the use of massage, heat, exercise, aspirin and coffee. The possible significance of these and other circulatory abnormalities frequently present in cases of arthritis (as described in previous Reviews) was discussed by Pemberton and Scull who again concluded that many of the symptoms of rheumatic diseases arise from disturbances of peripheral circulation and can be alleviated by correction of the latter. Schackle regarded capillary microscopy "disappointing" and of uncertain value (no details given).

*Factor of Altered Metabolism.* In the usual vague fashion some writers again spoke of the disease as caused chiefly by "deranged metabolism" from improper functioning of the digestive tract.<sup>40</sup> No new data were given to support the idea.

*Factor of Vitamin Deficiency.* Normal adults on a good diet excrete an average of 30 mg. of vitamin C in urine daily. The output of six patients with atrophic arthritis was "very low," an average of 15 mg. (Harc and

Williams). The vitamin C content of blood was lower in 26 typical and in 29 "less typical" cases of atrophic arthritis (range 0.09 to 0.68; average 0.23 mg. per cent) than in 120 control cases (range 0.22 to 1.45; average 0.7 mg. per cent) according to Rinehart and others.

When vitamin C was administered, the concentration in blood generally rose, sometimes very slowly, sometimes not at all. "Apparently deficiency of vitamin C may exist in atrophic arthritis in the presence of an ordinarily adequate dietary intake." Rinehart and his colleagues considered this deficiency an important factor in the etiology of the disease. The vitamin C content of blood was low (average 0.57 mg. per cent) in five "county cases" but normal (average 1.36 mg. per cent) in five "private cases" of Sherwood; therefore he considered a vitamin deficiency not the cause of the disease, but a factor which should be combated if present.

[Some of us have noted no appreciable effects from the use of large amounts of vitamin C.—Ed.]

*Factor of Food Allergy.* In a group of 150 cases which included cases of both atrophic and hypertrophic arthritis Pottenger noted a variety of "allergic manifestations," nasal allergy, asthma, canker sores, urticaria, migraine, and so forth, but especially "gastrointestinal symptoms from food allergy." For these and other reasons chronic arthritis was considered to be an allergic reaction to specific foods. An offending food presumably provoked gastrointestinal symptoms one to seven days after its ingestion and an increase of joint symptoms "a few days later after the disturbance in the gastrointestinal tract is established." The use of eliminative diets produced marked improvement in constitutional symptoms within five to seven days, in muscular and articular symptoms in another five to seven days.

[This report is unconvincing. No details on case reports and no clinical or laboratory evidence of improvement were given. The indiscriminate mixture of 95 cases of hypertrophic, 47 of atrophic and 8 of "mixed arthritis" confuses the issue still further.—Ed.]

*Intestinal Toxicosis.* Hepatic dysfunction was vaguely incriminated by some authors.<sup>84, 335, 720, 791</sup>

*Factor of Endocrine Abnormality.* No consistent thyroid abnormality was noted by Rawls, Ressa, Gruskin and Gordon: in 52 per cent of 141 cases metabolic rates were normal (— 10 to + 10 per cent), above normal in 23 per cent, below normal in 25 per cent. Rates varied with the activity of the disease. Rates may be increased in early active cases, but are reduced when the disease becomes chronic, and tend to be normal as the disease becomes less active. [Any coexistent thyroid deficiency should be corrected; some believe it may act as an important contributing factor.—Ed.] Without giving new data Cawadias supported the idea that the disease is related to ovarian deficiency.

*Neurogenic Factors.* Burt, Gordon and Brown examined 50 patients for nervous manifestations, especially abnormalities of the autonomic system. Acute or chronic worry or shock antedated the onset of the disease



[sometimes by 8 to 12 months, however.—Ed.] in 27 per cent of cases; in 73 per cent of this 27 per cent a sympatheticotonic reaction to the oculocardiac reflex was present. Vasoconstriction was present in 70 per cent of the 50 cases, but in some cases peripheral vasodilation and vagotonia, not sympatheticotonia, were present. The last is therefore only one factor in the composition of the pre-arthritic soil. Sweating occurred in 92 per cent; the colon was dilated slightly in only 10 cases, spastic in none. Blood pressures indicated only a mild sympatheticotonia. Oculocardiac tests indicated the presence of sympatheticotonia among 66 per cent of 50 arthritics and 40 per cent of 50 controls; vagotonia in none of the arthritics, in 16 per cent of the controls; normal tone in 34 per cent of the arthritics, in 44 per cent of the controls. But results of atropine tests to paralyze the vagus were not significantly different in the arthritics and controls. It was concluded that patients with atrophic arthritis exhibit slight but not clear-cut sympatheticotonia and no definite vagotonia; that is, they exhibit amphotonia or increased irritability of both divisions, as seen in psychoneurosis and certain other diseases. Thus "rheumatoid arthritis tends to occur in persons whose autonomic nervous system as a whole is irritable and unstable (amphotonic). Therapeutic correction of those disturbances will only reduce symptoms and not cure the disease."

The frequency with which emotional reactions could be correlated with exacerbations of atrophic arthritis and the importance of a strong religious faith or a positive philosophy of life to control the psychogenic factors of this disease were stressed by Swaim and Harris.

*Conclusions on Etiology.* To current students of the disease no one theory on etiology is proved satisfactorily as yet. The pathologic characteristics of the disease are of such a type that Ghormley<sup>355</sup> concluded their stimulus was "probably chemical rather than bacterial." Despite the implications afforded by altered sedimentation rates Kahlmeter concluded that the absence of significant alterations in total leukocyte counts or in the Arneth-Schilling blood picture is fairly strong evidence against the infectious hypothesis. "Infection if present—whether specific or not—merely plays the part of an exciting agent. This agent need not always be an infection." Edgecomb concluded that there are no constant metabolic changes in the disease and no evidence that any endocrine disturbance bears a direct causal relationship to it.

Having summed up in detail the case for and against the microbic theory Hench<sup>433</sup> made two conclusions, one as a clinical investigator, one as a practicing physician: "As a clinical investigator I must conclude that the cause of atrophic arthritis is still unknown and that the evidence for infection, although very impressive, is incomplete. Although the microbic theory seems attractive its weaknesses are apparent. The disease can be profoundly affected by non-microbic chemical alterations [incident to jaundice and pregnancy]. For these and other reasons, invoking the privileges of a clinical investigator I cannot and need not now decide for or against the microbic theory with any finality. As a practicing physician, however, I cannot wait until the evidence is complete. The exigencies of practice force one to express an opinion one

way or another. . . . Therefore as a practicing clinician I have committed myself, with reservations to the microbic theory." In comment thereon Edgecombe<sup>264</sup> stated, "With this conclusion, I think, most of us will agree" and Gibson<sup>358</sup> called it "a perfectly accurate summing up of the present unsatisfactory position."

#### RELATIONSHIP BETWEEN ATROPHIC ARTHRITIS AND OTHER DISEASES

*Rheumatic Fever.* On the basis of various clinical and immunologic data some authors<sup>371, 543, 937</sup> saw a close connection between atrophic arthritis and rheumatic fever. Findlay,<sup>309</sup> however, reviewing data for and against this idea, rejected the unitarian theory. Delatour never saw a case illustrating a transition between the two diseases.

*Still's Disease.* This will be discussed in a later section.

#### TREATMENT OF ATROPHIC ARTHRITIS

*General Remarks.* The treatment of this disease has varied "from the local application of rattlesnake or dog oil and salicylic acid to the injection of anything from salicylates, heavy metals and dyes, down to the removal of almost every organ in the body that is not padlocked."<sup>514</sup> Some physicians are distressingly pessimistic about the value of treatment. Since we know as yet "practically nothing" about the disease we remain, according to Shackle "but little advanced beyond Tom Brown's farmer, whose only infallible remedy for rheumatism was 'churchyard mould.'"

Others are more optimistic: it was White's<sup>1029</sup> opinion that "there is no chronic disease for which so much may be done." The ones to do it are the patient himself and his family physician because arthritis begins and ends in the home even if there is an interval of luxurious care in a hospital.<sup>450</sup> Hence a heavy responsibility rests on the shoulders of the general practitioner, who, although he produces no statistics, has no publicity agent and keeps his records, not on paper, but often only in his head, can often accomplish a cure by supervising simple forms of treatment in the patient's own home. Patients are in danger of falling into the hands of uninterested physicians who lack the necessary knowledge, perseverance and sustained interest.<sup>686</sup> Such physicians too often make but one therapeutic gesture (salicylates or tonsillectomy) and then abandon the case as hopeless. Or the patient may suffer at the hands of a so-called specialist who is "hipped" on his "method" which may utilize some one "specific." "Specifics" are usually of little value: an occasional brilliant result often is followed by many bitter disappointments. No patient should be treated merely as one of a "series of cases"; even mimeographed dietary directions should be discarded. Every patient should be treated as an individual problem and by a composite program, not by one favored remedy. "It is rarely necessary to inject several cubic centimeters of an expensive preparation into the buttocks to satisfy the patient's desire to have something done" (Myers). The disease should be considered a branch of internal medicine rather than of orthopedics.<sup>422</sup>

*Management of Foci.* The conservative removal of obviously infected foci was recommended again to improve the patient's general health. Very occasionally a "remarkable" <sup>952</sup> or "brilliant" <sup>918</sup> result is noted, but patients should be warned that such results are rare, and miraculous cures are not to be expected. <sup>422, 686</sup> Nevertheless some noted good results "too often to be coincidental." <sup>952</sup> A conservatively radical dental policy was currently advised. <sup>514, 531, 717, 851</sup> In the early stage of the disease Selig advocated the removal of all dental infection, including the removal of pulpless teeth or roots which give radiographic evidence of infection (but not those which do not). Others advised removal of all dead teeth and roots; in this disease all, not just some, pulpless teeth should be removed (O'Brien). But one should not expect a cure thereby. Improvement in arthritis was noted by McCollom in only 28 per cent of 46 cases in which tonsillectomy was done, in 30 per cent of 40 cases in which it was not done. Articular improvement was noted in 31 per cent of 29 cases in which infected sinuses were treated, in 23 per cent of 69 cases in which sinusitis was not present. In 6 of 12 cases of purulent sinusitis treatment of the sinusitis was followed by articular improvement. In general McCollom was disappointed in these results. Barwell considered tonsillectomy superior to diathermy coagulation: the latter method is at times useful but, contrary to the general notion, it is often difficult. According to Robinson most cases are due to cervicitis and in general the medical and surgical treatments used for it fail to remove the deep-seated infection. Robinson and Oldershaw recommended intrapelvic and intracervical diathermy, chief value of which is prophylactic. "The prevention of chronic infective [atrophic] arthritis in women lies largely in the hands of the obstetricians." At the hands of Robinson and Robinson such treatment produced marked improvement within five to nine months in cases of "infective arthritis" of less than 18 months' duration, but little or no improvement in cases of "rheumatoid arthritis."

[“Improvement within five to nine months” is not very striking; such slow improvement might well be coincidental.—Ed.]

Cecil and Angevine were not impressed with results from removal of infected foci. Tonsils were removed in 20 cases: in only seven was the disease benefited; in two it became worse and in 11 it was unchanged. Sinuses were treated in five cases and teeth removed in three without benefit. In many of these cases foci previously had been treated or removed: tonsils in 92 cases with no improvement in 86, exacerbations in two; teeth in 52 cases with no benefit in 47, exacerbations in three; sinuses in 12 cases with no benefit in 10, exacerbations in two. In view of these results the internist, not the "focal specialist," should decide what focus, if any, should be removed, and his attitude should be conservative.

[With this last remark we agree.—Ed.]

*Vaccines, Antigens, Filtrates.* The year's data on vaccines were meager. Of 50 patients to whom Breuer gave intracutaneous injections of autogenous

vaccines, presumably of hemolytic streptococci, 45 noted some degree of improvement; sometimes the amounts of the vaccine which gave relief were "so small as to appear ridiculous." Results were so impressive "as to make it difficult to restrain enthusiasm within scientific bounds." None of the other writers experienced this difficulty, but spoke of their results in more moderate terms. Keating noted better results from the use of autogenous vaccines made from streptococci agglutinated by the patient's serum, than from the use of those to which patients exhibited skin sensitivity but no agglutinins. Thompson, Wyatt, and Hicks considered a patient suitable for treatment with vaccine or antigen when sedimentation rates were high and agglutination titers low. Delatour's best results were with autogenous vaccines from hemolytic streptococci recovered from various foci including stools, to which patients were skin-sensitive (no results given). Attempted "immunization" against hemolytic streptococci seemed rational and beneficial to Hartung who gave intradermal and subcutaneous injections of a stock filtrate of a seven day broth culture. This preparation contains more of the exotoxins and decomposition products than a vaccine, and requires no further sterilization. The patients of Rawls, Ressa, Gruskin and Gordon who were markedly sensitive to vaccines, tolerated larger doses when thyroid extract was given.

Vaccines were considered of limited value by others and their results disappointing.<sup>450, 1029</sup> Cohn noted definite permanent improvement of only one of 74 patients given vaccines for six months. One great fault of vaccine therapy is that too many patients are treated by vaccines only for long periods, and gradually drift into a helpless, hopeless condition when other measures might have been employed usefully.<sup>204</sup> "Some dramatic results" with antistreptococcal serum given in normal saline solution per rectum were noted by Willcox (no details). Warner made a detailed critique on the subject of vaccine therapy in rheumatism. The use of large doses of vaccine has not proved of value. Desensitization should be attempted with small doses and focal reactions in joints avoided. "The principles of Warren Crowe's treatment [small *descending* doses] are in the right direction." Warner suggested that desensitization by oral methods may be of value. Vaccine therapy "may yet come into its own when used with greater skilled care and knowledge than has accompanied its use in the past."

[Some of us find it difficult to understand why vaccines should be expected to cure this disease of unknown origin when we know of no infectious disease of known etiology cured by vaccine.—Ed.]

*Foreign Proteins.* Only passing approval was given this form of therapy.<sup>254, 1029</sup>

*Chaulmoogra Oil.* A preparation containing "90 per cent chaulmoogra oil, 10 per cent olive oil and 2 per cent benzocaine" was used by Smith, Blocker and Tunen in 15 cases of atrophic arthritis and 33 of mixed arthritis: in 87 per cent of the former and 55 per cent of the latter symptoms

disappeared. The oil was injected intragluteally eight times in six weeks. It was rather irritating; one sterile abscess formed and required aspiration.

[One of us, J. A. K., has given up this remedy because of the severe pain produced by the injections and because significant results were not noted.—Ed.]

*Bee Venom.* An old popular European notion is that rheumatism can be cured by bee stings. Several injectable forms of bee venom have been produced recently: apicosan, apicur, apisin, British bee venom, immenin. Forapin is an ointment of bee venom, salicylic acid and oil of mustard. Bee venom is an albumin-free sapotoxin allied to snake venom, combined with a poison similar to cantharides. It contains no formic acid. Bee venom is supposed to act as a foreign protein, as a counter-irritant, as a desensitizing agent, or through a histamine-producing action. Burt could not prove the last effect. He noted good results in cases under two years' duration. Of 200 cases so treated, results in 50 were analyzed: 32 per cent of the patients were "very much better," 18 per cent were "better," 30 per cent were unchanged, 20 per cent were worse. Bee venom therapy is "by no means specific" but "of definite value in certain cases." Apicosan was used by Kroner, Lintz, Tyndall, Anderson and Nicholls in the treatment of 100 patients: none was cured, 35 were markedly improved, 38 moderately improved. Relief was "definite and lasting" and sedimentation rates fell. From 6 to 52 intradermal injections were given within 1 to 14 months. Untoward reactions occurred twice: severe urticaria and cellulitis necessitating surgical care. "Bee venom is worthy of further consideration."

[Results were not compared with any control series treated otherwise. We understand that this therapy is no longer used in the clinic where the work was done. One of us, W. B., has had very disappointing results with bee venom therapy.—Ed.]

This work was published in January; in September Nicholls, one of the co-authors, published a pessimistic report on results in 27 cases of treatment, not with injectable bee venom, but with the actual sting of honey bees. Five patients stopped treatments because they were "very disagreeable" or produced severe local or general reactions. Twenty patients accepted from 53 to 1,434 stings within 3 to 18 months. Three patients were "markedly improved and had remained well one year later," five were slightly improved, five unimproved and seven became "very much worse." Minor reactions were common: severe itching, rash, focal reactions in joints, severe headaches. "Bee sting therapy had no constant or noteworthy effect. Results were so discouraging that we felt we were not justified in continuing this form of treatment."

The results of Douthwaite with bee venom were "most unsatisfactory," those of Reichart (with "Apis D3") were good in fibrositis, "not encouraging" in arthritis (no details given). According to Kersley<sup>532</sup> the popularity of bee venom is decreasing in England; many think of it now only as a method of counterirritation.

*Diets.* There is no "arthritis diet" per se. The dietary prescription for each individual should provide for optimal nutrition, relief of constipation, and an abundance of vitamins and minerals, and should avoid foods to which patients may be sensitive.<sup>686</sup> A diet with carbohydrate restrictions seemed so important to Davis that he recommended that food should be weighed and managed with much the same accuracy as in diabetes. "The patient should weigh his own food, otherwise he will not follow the diet." Davis also recommended the use of an unnamed "seaweed preparation" as the best source of minerals since "ordinary vegetables are often deficient in minerals." Such a complex regimen found no other support. The diet usually approved for thin arthritics was one rich in calories, vitamins, and vitamin supplements, and low in starches; for obese arthritics one with caloric restrictions.<sup>952</sup> Most arthritics need generous amounts of proteins. "Acid-fruits" are *not* harmful: their organic acids, e.g., malic and citric, are completely oxidized in the body and excreted as carbon dioxide and water. Fruits are highly valuable sources of vitamins and minerals. Buckley deemed it wise to cater to the idiosyncrasies "commonly met with" in rheumatic patients. Strawberries, rhubarb, apples or cider were suspected of being irritating, especially to fibrositic patients. Even more strongly did Pottenger stress the supposed importance of uncovering food sources of gastrointestinal allergy. In rheumatism the saying "One man's meat is another man's poison" is particularly true, according to Kersley. One rheumatic may thrive on a diet of orange and tomato juice, while another may have an exacerbation from a tomato. But "if all the foods that may increase rheumatic symptoms were removed from the diet nothing but water would remain."

[We cannot approve the emphasis laid on the factor of food allergy in cases of atrophic arthritis; it is neither common nor do we consider it important. Variations in articular symptoms are so common from day to day that it is easy to blame erroneously some food for the day's ill-feeling. Cases of atrophic arthritis with undoubted and repeatable articular exacerbations from foods are few and far between.—Ed.]

*Vitamins.* Vitamin B. Supplements containing this vitamin are recommended<sup>264</sup> to correct the vitamin B deficiency of arthritis, and to prevent "neuritis" which may accompany gastric achlorhydria.

[We have never noted true neuritis in any of our patients with achlorhydria.—Ed.]

Vitamin C. In an unstated number of cases Rinehart and his associates noted "distinctly encouraging" results from the administration of the sodium salt of cevitamic acid intravenously and vitamin C orally (no details given). Hare and Williams gave six patients a diet rich in vitamin C and low in chloride; "an undoubted clinical improvement" was noted by all six, but that of the two who received 15 mg. of sodium chloride daily was less marked. It was suggested that the low output of chloride may have in-

fluenced a loss of fluid around joints. Blood chloride levels were constant. Supplementary feedings with vitamin C were approved by Sherwood.

Vitamin D. In the last review brief comments were made on the "remarkable" results which Farley claimed to have noted in 27 cases of chronic arthritis from massive doses of vitamin D. Farley has continued his paeon of praise for this mode of therapy as, "a weapon effective in every type of arthritis, regardless of the state or advancement of the disease, a weapon so powerful that it often accomplishes dramatic results *in the end stages* [*italics are ours.—Ed.*] of arthritis, after practically all other means of therapy have proved of no avail." To 87 patients with "arthritis" he has now given from 50,000 to 1,000,000 U.S.P. units of vitamin D [ertron] daily: optimal doses, those tolerated without toxicity, varied from 150,000 to 500,000 units daily. "Every patient responded well to the management established, unfavorable results did not appear in a single instance."

[No details whatsoever were given regarding 84 of the 87 cases. Only 3 brief case reports were noted. No attempt was made to classify the types of arthritis treated. The reader is asked to accept the writer's practically unsupported word as to these wonderful results. The wording of the report is, to say the least, incautious, and the results are quite at variance with those reported by others including the originators of this form of therapy. Reports of this kind are bound to lead to serious disappointments by others, add to the cost of treatment, and may indeed lead to dangerous effects for patients.—Ed.]

In sharp contrast to Farley's report were two others, one by Steinberg and one by Abrams and Bauer. Steinberg generally gave 160,000 U.S.P. units daily to 29 patients with atrophic arthritis: "10 showed clinical improvement and 19 showed no improvement whatever." The influence of the vitamins on blood calcium and phosphorus was studied in 12 cases. No marked hypercalcemia developed. These doses first raised a low or normal serum calcium to a higher level, later the hypercalcemia decreased. Calcium levels in blood bore no relationship to symptomatic results: no untoward results occurred. "No specific virtue exists in such medication." From 80,000 to 160,000 U.S.P. units of vitamin D (Drisdol in five cases, crystalline vitamin in others) were given daily by Abrams and Bauer to 18 patients with atrophic arthritis. Subjective improvement, lasting through the period of treatment, was noted in eight cases, in only three cases was there objective improvement and in only one was it marked. When therapy was stopped the improvement was short lived. Significant reductions in sedimentation rates were noted in only five cases, in only two of which was improvement subjective and objective. Hypercalcemia (up to 16 mg. per cent) developed in 16 of the 18 cases. Toxic symptoms frequently occurred. It was concluded that massive doses of vitamin D are "of little or no value in altering the course of this disease. The general effects of the larger doses do not appear significantly different from those observed with the usual therapeutic doses, and do not justify the expense and dangers involved."

On the basis of their results as a whole, Abrams and Bauer are justified in their conclusions. But in at least one case (No. 286) a marked subjec-

tive and objective improvement occurred, lasted only a few weeks after medication was stopped, and recurred definitely but less notably when medication was resumed.

[Two of us, W. P. H. and A. J. K., have noted such an effect sufficiently often to recommend further consideration of this therapy as a research investigation, but not as a remedy suitable for general practice.—Ed.]

The use of cod liver oil, plain or with malt extract, in ordinary doses was recommended; if the oil cannot be tolerated, viosterol (irradiated ergosterol) or radiostoleum (5 drops t.i.d.) is used (Ellman).<sup>282</sup>

*Additional Intestinal Therapy.* Salol (phenyl salicylate) or guaiacol were recommended as "intestinal antiseptics."<sup>233, 245</sup> According to Douthwaite many patients exhibit an excess of gastric mucus, the result of chronic gastritis, which lowers the free acid in gastric juice. "If these stomachs be washed out with peroxide of hydrogen and water so that excess mucus is removed, a further test meal may reveal a normal acid curve." Some prescribed hydrochloric acid for patients with gastric hypo-acidity, but others<sup>254</sup> noted no dramatic results therefrom. Constipation should be controlled by diet, habit-time, abdominal exercises and massage. If necessary, an occasional high colonic injection, an enema of salt solution or small injections of oil can be used and are preferable to the habitual use of cathartics according to Keating. Repeated colonic injections are harmful.<sup>245</sup> White permitted the use of a mild laxative daily, cascara and oil, or heavy calcined magnesia. That preferred by others<sup>40</sup> was a full glass of tepid normal salt solution taken early in the morning. Assuming that a hepatic dysfunction exists in this disease O'Connor frequently gave calomel followed by a saline cathartic to "assist the liver in its detoxicating function." Such measures were approved by van Breemen: "It is well known that quacks frequently attain success in chronic rheumatism because they prescribe starvation diets and strong purgatives much more frequently and with greater skill than do medical men."

*Miscellaneous Medicines and Other Substances.* There is no drug known to have a direct influence on the joints in arthritis.<sup>315</sup> Hence the rôle of drugs is limited "but not unimportant."<sup>282</sup> For pain, aspirin (45 to 60 grains daily) was considered best, but one should "give enough." Antipyrine was recommended also. When pain is severe the occasional use of 1/10 grain of dilaudid with 10 grains of phenacetin seemed permissible to Douthwaite. Dilaudid is a morphine derivative, dihydromorphinone hydrochloride. For sleeplessness caused by pain 10 to 15 grains of aspirin at night with a sedative were given. For sleeplessness not caused by pain 15 grains of bromide with 10 grains of chloral flavored with syrup of tolu seemed preferable to barbiturates. To counteract the distressing fatigue of arthritic patients the use of elixir glycocoll (amino-acetic acid: glycine) "serves admirably" (Lautnan), and Douthwaite found benzedrine sulfate "remarkably efficacious" (20 mg. in the morning and just after lunch but none after 2 p.m. lest insomnia be produced).



[The latter has an ephedrine or adrenalin-like effect, objectionable to some. The matter of dosage must be individualized, that amount being used which will relieve fatigue but not produce nervousness or insomnia. It should be used occasionally, not habitually, and with discretion.—Ed.]

Thyroid extract. In cases of atrophic arthritis associated with hypothyroidism (these are not common) the use of thyroid extract has been considered useful: "Remarkable reduction of joint swelling and an immensely improved range of joint movement frequently result" (Ellman). But Rawls and his associates were not impressed with it. "Only 20 per cent of patients with markedly active rheumatoid arthritis showed improvement." Many patients could tolerate only small doses, and in some cases it had to be discontinued. Some patients noted improved appetite, euphoria and "increased resistance to infection." [How measured?—Ed.] But joint symptoms and metabolic rates were not affected even though the latter were subnormal.

Insulin. Ellman gave again his scheme of insulin therapy to counteract anorexia and loss of weight (5 to 30 units daily for two to three months).

Progestine. To three patients (two with "primary chronic polyarthritis," one with "secondary osteoarthritis deformans") whose articular symptoms were markedly benefited during pregnancy Touw and Kuipers gave "2 c.c. progestine (10/E)" intravenously daily for 10 to 11 days during the second two weeks of the intermenstrual period. After two or three such courses 2 of the 3 patients noted marked relief of articular symptoms; the third patient received only one course and was less notably benefited. Pregnyl ("1,000 E. daily") was ineffective.

[One of us, W. B., has given progynon 10,000 rat units biweekly for months in cases of atrophic arthritis without effect. In two of these cases an additional 10,000 rat units was given daily for 9 and 10 days respectively also without effect.—Ed.]

Amniotic fluid concentrate. This substance when injected intraperitoneally is said to prevent or minimize formation of adhesions. According to Schimberg its intra-articular injection hastens a defense-repair mechanism within joints, successfully prevents the formation of new adhesions after closed manipulation of joints, is a valuable prophylactic after arthrotomy, and produces no untoward reactions. Results obtained in intra-articular fractures were "impressive," those in selected cases of atrophic arthritis and persistent joint effusion were "encouraging." In six cases of subacute atrophic arthritis effusions were withdrawn and replaced with a larger volume of the concentrate on from two to seven occasions; results were "satisfactory," the symptoms cleared up, and during the period of hospitalization the improvement was maintained.

[One of us, M. H. D., obtained some amniotic fluid concentrate (amfetin); but since it appeared to contain little or no protein and no carbohydrate, it was regarded as biologically inert.—Ed.]

Lactic acid (intra-articular injections). Encouraged by his results noted under "Treatment of traumatic arthritis," Waugh made similar injections in five cases of atrophic arthritis, since the synovial fluid was abnormally

alkaline ("pH 8 and over"): "All derived much benefit." One case in which the result was especially gratifying was reported in detail.

Procaine. Considerable analgesia has presumably resulted from intra-articular and periarticular injections of procaine in various arthritides. Tarsy used procaine hydrochloride, 1 per cent solution, in most cases, eucupine oil in others. Results were "not as good" in the progressive infectious arthritides as in the degenerative or traumatic forms, but "exceptionally good results" were noted in "several" cases of atrophic arthritis despite the fact that "in the main, results have not been gratifying."

Miscellaneous. The supposed indications for and value of the following were discussed: arsenic, strychnine, quinine, calcium, iodine, and calcium or ammonium orthoiodoxybenzoate.<sup>233, 254, 282</sup>

[Editors of symposia on rheumatic diseases frequently ask physicians to write on the use of drugs for these conditions. Despite the fact that the value of drugs is limited, the physician writing such a chapter often attempts to make a "decent showing" in their behalf, with the result that he is in danger of recommending a whole pharmacopoeia rather uncritically, if not actually *con amore*. The recommendations of an "authority" under such circumstances too often perpetuate false ideas on the value of these medicines in arthritis. Patients are then likely to use them for a long period to the exclusion of much more important measures.—Ed.]

And now for some pharmaceutical "step children."

Causalin (aminodimethyl-pyrazolon-quinoline-sulphonate). Kimble was the year's torchbearer for this remedy. In 36 of 56 cases of "chronic nonspecific arthritis" treated therewith either "marked improvement or complete remission of symptoms" occurred.

Arthranol (amino-salicyl-phospho-benzoyl-iodide). Mingled with some philosophy and morality was the recommendation of Stern and Kurland for this substance: "Our results were over 90 per cent successful in our arthritics."

[One wonders whether the "before and after photographs" showing improvement in articular function and posture were taken really before and after a course of treatment or at the same photographic sitting.—Ed.]

Subenon ("calcium double salt of benzoic and benzyl succinic acid"). With this substance, Leir treated "all types of arthritis." He stated: "Within a comparatively reasonable time after subenon was administered, a large percentage showed varying degrees of improvement, in some cases exhibiting a restoration that was most gratifying." Supposedly corrected was some vague gastrointestinal dysfunction presumed to cause arthritis.

Arthox ("sulfiodoxygenia"). This "patent medicine" once contained sodium salicylate and many other substances supposedly good for arthritis, rheumatism and muscular aches. Later, it was found to contain as its essential ingredients sulfuric acid, sodium iodide, flavoring substances and probably colchicine. The manufacturers must have run out of salicylates! In other words "when one buys a 'patent medicine' one buys a name and not a thing."<sup>140</sup>

Transfusions; hematronics. For cases of significant anemia large doses of iron and transfusions have been recommended. According to Atsatt and Ussher the anemia should be vigorously combated (by the usual hemogenic agents plus liver extract as needed) because "ofttimes the whole success of treatment may hinge upon the up-building of the blood picture." Douthwaite considered the treatment of the anemia "a simple matter seldom needing more than the administration of iron in adequate doses." Freshly prepared Bland's pills (50 grains daily) were "highly effective" but sometimes produced indigestion and constipation. Blood transfusions rarely were considered necessary. Hartung's view was that, unfortunately, the anemia is caused mainly by the disease itself, so that the hemoglobin can be raised only with the greatest difficulty. "Transfusions likewise have only a temporary effect but are invaluable in giving the patient that lift which sometimes means the onset of recovery." They were considered "extremely useful" by Thompson, Wyatt, and Hicks who gave 198 of them to 48 patients (average of 4 transfusions per patient, each 300 to 600 c.c., at intervals of two to six weeks). "Improvement" was noted in 66 per cent of cases; subsequent sedimentation rates were frequently halved.

[Although slight or moderate reductions in hemoglobin and erythrocytes are common, marked deficiencies are rare. "There is no foundation for the suggestion that anemia may be the causal factor" (Shackle). Under the mistaken idea that "If we can only build up the system and correct the anemia, the joints will take care of themselves" too many physicians treat the anemia strenuously, usually without notable success, and neglect more important measures. It is more correct to say, "Treat the arthritis and the anemia will care for itself." Of course significant anemia should be treated, but dramatic results are not to be expected.—Ed.]

Sulfur. This remedy for arthritis has about run its span of favor. Nothing good was said of it. "The results are essentially nonspecific"<sup>254</sup> and "disappointing."<sup>252</sup> "Sulfur injections do not seem to fulfill claims made for them."<sup>254</sup> The Council on Pharmacy and Chemistry<sup>228</sup> of the American Medical Association after reviewing 42 articles thereon, accused the proponents of this therapy for arthritis of having been uncritical in their judgment, careless in the details of their cases, negligent about the proper typing of the cases of "arthritis" under treatment, and not sufficiently sure of the indications, contraindications or proper dosage of sulfur. "Not one of the leading arthritis clinics of the United States has adopted the use of sulfur in the treatment of arthritis so far as can be determined." The Council concluded, "It is unsuited for experimental use except in institutions, or under other conditions in which its effects may be followed intelligently and accurately for prolonged periods."

*Gold Salts: Chrysotherapy.* Several new English but no detailed American reports on this form of treatment appeared. Although the treatment is empirical, it was called "the greatest step forward in therapeutics since the disease was first described" (Douthwaite), "a method which gives results incomparably better than any obtained hitherto" (Stone).<sup>218</sup>

**Preparations.** The gold salts used in these reports were myochrysine (van Breemen), solganol 'B' (van Breemen; Stone), allochrysine (Stone), sanocrysin (Secher), and a new one, parmanil (Bayer) (Hartfall, Garland and Goldie).

**Indications.** Suitable for treatment are any active cases of atrophic (rheumatoid or chronic infective) arthritis with no obvious renal or hepatic disease or history of purpura.<sup>253, 918</sup>

**Contraindications.** The presence of definite renal or hepatic disease, a personal or family history of purpura or other blood abnormality (except mild secondary anemia) was considered an absolute contraindication for this treatment.<sup>283, 284, 918</sup>

**Results.** Two English and one American commented unfavorably. Willcox said, "I do not like to use gold salts," because of the risk of complications. Another physician<sup>539</sup> wondered whether the only real use for gold in this disease was the transference of gold from the patient's pocket to that of the physician. The results of Thompson, Wyatt and Hicks were "disappointing" (no details given). But van Breemen was "very satisfied" with results in about 300 cases: "The results surpassed those of any other therapy." However, he considered it "extremely dangerous." Without giving details of his own results Stone considered gold therapy "unquestionably the most valuable therapeutic measure discovered so far. Dramatic cures are sometimes obtained, while relief of pain, swelling and stiffness is so common that the efficacy of gold can scarcely be doubted." Despite these good results Stone also called it "a dangerous drug." Of patients so treated pains may begin to lessen after only a few injections or not until over 1 gm. has been given, sometimes not until two or four weeks after the first course.<sup>253</sup> Sedimentation rates generally begin to fall after two or three injections, but there is often an initial rise after the first month of treatment.<sup>283</sup>

A serious criticism of almost all previous reports has been that no observations on controls were made. These have been made now by Ellman, and Ellman and Lawrence. Ellman gave injections of gold to 24 patients with "infectious arthritis" and of almond oil to 14 arthritic controls. Beneficial effects were noted by both groups but especially by those receiving gold: three of the latter but none of the controls were cured. Later Ellman and Lawrence treated three groups, of 20 patients each, by sterile oil, small doses of gold (maximal dose 100 mg.) and large doses of gold (maximal dose 200 mg.). The records of subjective improvement were fortified by measurements of actual articular sizes and of sedimentation rates.

Results are given in table 2.

Thus gold, in large and small doses respectively, cured 10 and 6 times as many as the oil injections. Hence it was concluded that the effects of gold were not merely psychic, and that chrysotherapy was a distinctly superior form of treatment. "The effect of gold is to hasten the course of the disease by producing first an aggravation, then a gradual improvement so that

TABLE II  
Results in Percentages

Result	On Large Doses of Gold (20 Cases)	On Small Doses of Gold (20 Cases)	Controls on Oil (20 Cases)
Cured.....	50	30	5
Improved.....	45	60	65
Not improved.....	5	10	30
Joint swellings reduced.....	81	79	16
Sedimentation rates reduced to normal.....	74	40	15

the inactive stage is reached in one year instead of in 20 to 30 years as is often the case without gold."

Having previously treated the enormous number of 1200 cases with various gold salts, Hartfall, Garland and Goldie used a new "equally effective" and less toxic preparation, parmanil, in the treatment of 50 patients, 21 of whom had had the disease five or more years.

Parmanil (Bayer) is an oily solution for intramuscular use, the methyl glucamide of auro-thio-diglycollic acid; its total gold content is 50 per cent. Weekly injections were given, beginning with a dose of 25 mg. and increasing to 100 mg.; total dose for a course was 600 mg. given in about 12 injections. One course was given to 31, two to 19 patients. Of the 50 cases, cures resulted in 4 per cent, marked improvement in 84 per cent, moderate improvement in 6 per cent, slight improvement in 2 per cent, none in 4 per cent, deaths in none. These results were compared with those noted in 690 cases treated with older gold salts, in which cure resulted in 10 per cent, marked improvement in 57 per cent, moderate improvement in 13 per cent, slight in 6 per cent, none in 11 per cent, death in 3 per cent (19 cases). Thus although cure was achieved in only 4 per cent by parmanil and in 10 per cent by other salts, parmanil produced marked improvement in many more cases. "The results with parmanil are as good, if not better" than those from four other gold salts (lopion, solganol B oleosum, crisalbine, myocrysine or myochrysine). The doses of parmanil were smaller than those of some salts, about equal to those of lopion: the latter produced no cures, marked improvement in 41 per cent of cases, as compared to cures or marked improvement in 88 per cent of cases in which parmanil was used. Toxic reactions from parmanil were slight in 14 per cent, moderate in 6 per cent, severe in 6 per cent (total 26 per cent) and absent in 74 per cent of cases. Compared to reactions from other salts these figures indicate that parmanil is perhaps the least toxic of the gold salts.

[Although the total percentage of toxic reactions from parmanil was lower than that from other salts, the percentage of *severe* reactions was about the same. Thus severe reactions occurred from crisalbine in 5 per cent, lopion (large doses) in 4 per cent, solganol in 2 per cent, myochrysine in 6 per cent, parmanil in 6 per cent, lopion (small doses) in 3 per cent of cases so treated.—Ed.]

*General plan.* The plan was to give injections of gold every five to seven days; initial dose was 10 mg., subsequent doses 20, 50 and 100 mg., maximal single dose 100 mg., total dose for one course 1 gm.<sup>918</sup> Douthwaite gave, in acute cases, 10 mg. for each of three doses, then if no reactions occurred, 50 mg. for each of six doses, then 100 mg. doses thereafter until 1.5 gm. of solganol or myochrysine was given, or 2 gm. of allochrysine; in less acute cases six or seven doses of 50 mg. each, thereafter 100 mg. each dose. The schemes of Ellman and Lawrence were different. Patients given the "larger doses" received 10, 50, 100 and thereafter 200 mg. each dose

up to a total of 2.5 gm. But those given the "smaller doses" received 10, 20, 40, 75, and thereafter 100 mg. each dose until the sedimentation rate fell below 10 mm. (1 hour). To accomplish this the weekly doses were often continued uninterruptedly for nine to twelve months. According to Ellman and Lawrence no harm results from prolonging the first course no matter how large the total dose of gold given, provided the sedimentation rate remains high and the leukocyte and platelet counts are satisfactory. "The present practice of limiting the first course to one gram is likely to lead to numerous failures." Six weeks after the end of the first course, they began the second course, this time with 50 mg. as a maximal dose.

The number of courses required was "always two, generally not more than three or four" (Stone), "usually four to six" (Douthwaite). Intervals between courses were two to three months (Douthwaite), three months (Stone), six weeks (Ellman and Lawrence).

**Toxic reactions.** These are common, occasionally serious or even fatal and provide the great drawback to chrysotherapy. Because of them the drug was called even by its proponents, "extremely dangerous." These reactions were discussed in some detail in previous Reviews<sup>4, 5</sup> and include giddiness, headache, vomiting, abdominal pain, diarrhea, focal reactions in joints, fever, stomatitis, jaundice, albuminuria, various skin reactions from herpes to exfoliative dermatitis, colitis, proctitis, rarely neuritic and ocular lesions (conjunctivitis, phlyctens). The most disturbing reaction is exfoliative dermatitis, the most severe is agranulocytosis.<sup>214, 253, 283</sup> Use of the drug should be stopped if the following occur: erythema with slight fever (this may be a forerunner of exfoliative dermatitis), significant albuminuria, stomatitis, dermatitis of squamous or exfoliative type, hepatitis or jaundice, blood dyscrasias (purpura hemorrhagica, agranulocytosis, aplastic anemia, marked fall in blood platelets<sup>348</sup>). Blood dyscrasias generally occur, if at all, late in treatment. Agranulocytosis must be considered an idiosyncrasy, not a sign of metallic toxicity. According to Secher most of the reactions are not due to metallic intoxication but to toxins liberated from the affected tissues themselves. In four of their 60 cases Ellman and Lawrence noted stomatitis, in six exfoliative dermatitis, in one case agranulocytosis.

**Treatment of toxic reactions.** This is purely symptomatic. Sodium thiosulfate is now considered useless.<sup>283, 284, 348</sup>

**Prevention of toxic reactions.** There is no known certain method of preventing them. One should adhere to the contraindications, examine skin and urine weekly, make blood counts (especially leukocytes and platelets)<sup>348</sup> at least every two or three weeks, and discontinue, at least temporarily, the injections at the first sign of any significant reaction, some say at the first sign of any reaction however slight.<sup>918</sup> Calcium gluconate is considered of no prophylactic value. If the drug is stopped on the appearance of a metallic taste, stomatitis may be avoided.<sup>214</sup> Eosinophilia is said to precede dermatitis, but usually too closely to be a useful warning.<sup>214, 849</sup> But eosinophilia is a fairly frequent feature of the disease itself and not just a sign of gold toxicity although it is aggravated by chrysotherapy.<sup>283, 284</sup> A rather sudden change from leukocytosis to leukopenia may signify impending dermatitis.<sup>214</sup>

Since the severe toxic reactions generally occurred, not when sedimentation rates were high, but toward the end of a course when rates were no longer high, it appeared to Ellman and Lawrence that patients with an elevated rate were more immune to toxicity than those with normal or almost normal rates. Hence they recommended that the dose be reduced to 30, 10 or even 5 mg. when sedimentation rates approach 10 mm. (1 hour). Secher claimed that the severe toxic reactions can be prevented or checked by the vigorous use of vitamins A, B and C. Beginning a few days before gold was given he gave daily vitamin A 20,000 international units, vitamin B 750 to 1500 international units, vitamin B<sub>2</sub> 375 to 750 Krieger Lassen units, vitamin C 2500 international units. "The results so far have been excellent"; no difficulty of any kind occurred during treatment in 150 cases.

[These doses of vitamins would cost about 15 to 20 cents daily. If they really will prevent serious toxicity from this therapy they are certainly worth it.—Ed.]

*Vasodilators: Histamine, Choline.* The use of histamine by injections was considered by Douthwaite to be of definite value in certain cases with vasomotor changes but little deformity. The effect of each injection lasts only from a few hours to two or three days. Nevertheless sometimes "it may act like a charm; I have known patients who had become, one might say, histamine addicts so great was the relief they received." But in most cases the results are "transient and disappointing." Histamine was used by Stormont as an ointment, "imadyl," with presumed benefit.

The use of mecholyl iontophoresis (acetyl beta methylcholine chloride) was approved in various types of arthritis, including atrophic (Bredall). Neuberger and Scholl (1937) reported that subcutaneous injections of acetylcholine prevented the ankylosis and muscle atrophy which normally follows experimental immobilization of the limbs of animals. As a result of experiments on 12 rabbits Harvey could not confirm this report: the drug did not prevent the results of immobilization.

*Sulfanilamide.* Of 13 patients given sulfanilamide by Koerner and Poulton seven noted "improvement." But the results were not striking. From 25 to 50 grains daily were given for three or more weeks. Several patients treated by Finn seemed to be benefited, especially those with the more acute condition (no details). But Simmons and Dunn were "not impressed with its value in atrophic arthritis" (no details). Bauer and Coggeshall gave large doses to 10 patients without affecting sedimentation rates or the course of the disease: "the agent responsible for rheumatoid arthritis is not susceptible to this type of therapy." In two cases of rheumatoid arthritis nonfatal agranulocytosis developed after seven and 30 days of this therapy.<sup>23,645</sup>

*Bile Salts; Bilirubin, Artificial Jaundice.* For years certain physicians have tried to connect atrophic arthritis with some vague hepatic deficiency, or perhaps a hepatic dysfunction in the nature of a failure of the detoxifying function of the liver. But the idea has been incapable of proof since no

significant pathologic lesion in liver has been noted and a few studies with different tests of hepatic function have shown no consistent hepatic insufficiency (Watson, 1928; Rawls, Weiss and Collins, 1937). However, this notion is the basis of the French concept of "arthritism"<sup>84</sup> and the possible connection was mentioned in passing by current writers.<sup>335, 720, 791</sup> Recent observations on the ameliorating effect of jaundice on atrophic arthritis seemed to suggest, perhaps more definitely than heretofore, that there was some direct or at least indirect connection between atrophic arthritis and the liver. Hench<sup>430, 432</sup> therefore made various attempts to reproduce the analgesic effect of spontaneous jaundice by using bile and related substances. No significant results were noted by him from the use of bile salts (glycho-tauro, oxgall), or synthetic bile salts (decholin, sodium dehydrocholate) given orally, large amounts of human bile given by stomach tube (up to 2,600 c.c. in one day or 7,650 c.c. in 10 days) or ordinary liver extracts. A few patients were given one to four transfusions of fairly large amounts of highly jaundiced blood (up to 800 c.c. of blood containing 21 mg. of bilirubin per 100 c.c.). One patient accepted experimental jaundice induced by toluylenediamine. No significant effect on joints was noted from these procedures. For reasons stated in his paper injections of bilirubin were not given.

Later, Thompson and Wyatt noted that the intravenous administration of bile salts alone (decholin, 2 gm. daily for 9 to 12 days) had no effect on atrophic arthritis, nor did injections of bilirubin alone (10 to 15 mg. per kilogram daily for several days) in three cases. But they reported that injections of bilirubin (10 mg. per kilogram) and "decholin" (40 mg. per kilogram) in combination produced an ameliorating effect "which apparently duplicates the effects" of spontaneous jaundice. The injections produced no significant toxicity and no definite evidence of hepatic or renal dysfunction. They were given to 10 patients daily for 7 to 11 days. Definite icterus and hyperbilirubinemia were produced (concentrations of serum bilirubin rose to between 19 and 35 mg. per 100 c.c.). After several doses articular pain and swelling diminished in varying degrees and for variable periods (in one case for 5 months, in another for 5.5 months, in others for 2, 1 and 1 months respectively). Five patients were still free of pain at the time of the report. Jaundice had disappeared from 14 to 23 days after the last dose. Five months after the first report Thompson and Wyatt<sup>951</sup> noted the further effects of this form of artificial hyperbilirubinemia in a total of 16 cases in each of which an average of nine doses of the bilirubin-decholin mixture (from 7 to 12 injections) had been given. Of the 16 patients 14 experienced variable amounts of relief (analgesia and diminished articular swelling). Eight patients had "short" remissions (5 to 45 days), six had "long remissions" (2 to 13 months). The relief was complete in some cases, partial in others. Two patients noted no relief. Results bore no direct relationship to the degree of induced jaundice. Thompson and Wyatt concluded that it was possible to inactivate atrophic arthritis in this manner



more rapidly than by any other measure, and that the inactivating effect of this "artificial jaundice" was similar to that from spontaneous jaundice.

Hench was unable to corroborate this work in toto. To 11 patients with atrophic arthritis (and one with primary fibrositis) he gave 12 to 20, in some cases 25 to 30 daily intravenous injections of the bilirubin-decholin mixture. Rather intense degrees of visible jaundice were induced by daily doses, generally of 15 mg. per kilogram of bilirubin and 40 mg. per kilogram of decholin. Among the 12 cases little or no relief was noted in five, short incomplete remissions resulted for a few days only in six; one patient had a rather complete remission of symptoms which lasted only three weeks, the longest, most definite effect noted. Three slight changes in technic made by Hench seemed of possible significance to Thompson, but insignificant to Hench because results were no better when the differences were corrected. Hench concluded that by this means an obvious and apparently harmless bilirubinemia or "artificial jaundice" can be produced, the effects of which are not nearly as striking as those of spontaneous jaundice.

[In its present form the procedure is impractical, expensive, rather laborious, and inconstantly and incompletely effective. It is certainly not a practical "control of arthritis"<sup>1052</sup> and should be considered strictly a research procedure. But the fact that the disease can be modified at all by such a novel and unorthodox method seems significant and affords further evidence that the disease may some day be made rapidly "reversible," at will. The work offers a wide field for speculation as to the possibility of discovering the agent responsible for the remissions induced by jaundice and utilizing it in the field of therapy.—Ed.]

The fact that jaundice should beneficially affect rheumatic patients seemed rational to Najib-Farah. Having discovered (1934) pneumococci in cultures of the blood of a patient with subacute rheumatic fever, he concluded that rheumatic fever was caused by pneumococci. He more recently has interpreted the bilirubinemia, which occurs not infrequently in pneumococcic and typhoid infections, not as evidence of impaired liver function but as a protective mechanism designed to overcome infection. According to him<sup>693</sup> bilirubinemia plays an important rôle in the processes of defense and immunity of the organism.

[It is reported<sup>967</sup> that jaundice affects 5 to 10 per cent of cases of lobar pneumonia in whites, a much higher (78) percentage of negroes. The lighter form of jaundice is said to have no significance, the deeper forms are reputed to be associated with toxic hepatitis and a grave prognosis. Were Najib-Farah's conception correct would not the prognosis be better in the presence of severe jaundice, and were acute and subacute rheumatism due to pneumococci would not sulfapyridine be highly effective?—Ed.]

*Cystein.* Shipton and Parr suggested that the beneficial results of jaundice and pregnancy might be related to retention or increased formation of one of the amino acids, perhaps cystein, during these states, also that the beneficial effect of operative procedures on atrophic arthritis may result from excessive autolysis of tissue protein, the sources of amino acids in the body being digested food protein, and autolysed tissue proteins. Hence an amino acid, histidine, was first given to arthritics (number unstated); "only one case out of three" was benefited. But when intramuscular injections of cystein (0.2 gm. daily) were given in two severe

cases of atrophic arthritis with marked skin atrophy, a "rapid and definite effect" was seen.

[The results are not very impressive; the first patient was given two periods of starvation of four days each just before administration of cystein was begun, and although "dramatic improvement" occurred it was deemed necessary later to commence gold therapy. In the second case also cystein was used with other measures.—Ed.]

*Rest and Movement.* Rest was called "the keystone of treatment"<sup>539</sup> and, "the most important single factor in treatment"<sup>686</sup> but one which should not be overdone. The patients should rest prone one hour after each meal with joints in the position of least strain. This can best be done by the use of splintage in light plaster shells.<sup>539, 758</sup> Rest in these moulds relieves pain and reflex muscle spasm and prevents deformity therefrom.<sup>918</sup> But complete rest must not be continued for more than a few (at most seven) days.<sup>539</sup> Prolonged complete rest is as dangerous as the advice often given to patients to "walk it off" or "keep about at all costs." An adequate range of articular motion must be maintained even during rest to sustain and improve muscle and joint function. Joints should be exercised within limits of their tolerance. Both rest and exercise should be prescribed in exact doses. Bradford outlined a system of exercises useful for bedridden as well as ambulatory patients; they should be instituted long before the patient is ready to get out of bed.

*Physical Therapy.* A great many physicians know little or nothing about physical therapy, others regard it as a not quite respectable stepchild of medicine. To raise physical medicine to its proper status is the aim of the American Academy of Physical Medicine and the American Congress of Physical Therapy. The ideals of these organizations were well stated in addresses by their Presidents Lowry and Krusen, respectively. They propose to promote proper teaching of physical medicine in medical schools, to combat unjustifiable claims, promoting at the same time valid claims; they seek to avoid commercial taint, to establish physical medicine on sound principles. Krusen made certain recommendations designed to improve the scientific reports of physical therapists. Such therapists should avoid the spectacular, avoid half-truths and overenthusiasm, and correct the inadequacies and inaccuracies too common to the literature of their specialty. Brief general articles outlined the technic, indications and contraindications for the various types of physical therapy<sup>63, 64, 238, 551, 755, 756</sup> and their physical (Taylor) and physiologic basis (Hill). Rather than apply these methods haphazardly and unintelligently physicians not trained in their administration, should refer patients for treatment to those who have been trained, but both physician and physical therapist should coöperate closely.<sup>657</sup> Physicians should try to select the form of therapy most suitable for each patient and should review their patient's condition at least after every 12 treatments to see whether the therapy should be changed to get better re-

sults.<sup>64</sup> Patients should be taught as supplements the simple inexpensive methods available for use in the home.<sup>738</sup> The physiologic effects of heat were noted,<sup>63</sup> also indications for the various types of light therapy (Eidenow). The simple infra-red lamp is "the best source of heat (Krusen)."<sup>551</sup>

The technic of contrast baths differs in various clinics: in many the alternating applications of hot and cold were given empirically for one minute each. Pennington used applications of three minutes each but considered them unsuited for patients with impaired peripheral circulation. Woodmansey, Collins and Ernst made an interesting study on the physiologic responses of different "normals" and patients with atrophic arthritis to contrast baths of different lengths.

Temperatures of the hot water were from 107 to 113° F., of the cold water, from 47 to 55° F. The time of the hot and cold applications was changed about to note what combinations induced the optimal response in peripheral circulation. Changes in the skin temperatures of extremities were recorded before, during and after the treatments. Ten healthy males produced the best type of circulatory response, skin temperatures went upward rapidly in a remitting or steplike fashion, indicative of rapid adaptability. It was found that when the common (one minute hot and one minute cold) technic was used, even the most responsive normal subjects failed to respond satisfactorily, the alternating periods were too short. Sometimes the technic resulted in an actual composite fall rather than rise in skin temperature. Responses were satisfactory with five minutes in hot and five minutes in cold water, and with seven minutes in hot and three minutes in cold, but the use of six minutes in hot and four minutes in cold water was the most comfortable for patients and gave rise to the best warming effects. Some healthy women and patients with atrophic arthritis responded abnormally to this scheme. In cases of active severe arthritis the "worst responses" were encountered: temperature curves revealed practically no local vascular reactions and a progressive cooling rather than a net warming of the extremity.

Since no male arthritic patient exhibited poor reactions, no evidence was obtained to suggest that atrophic arthritis is grafted on a preëxisting vascular dysfunction. The sluggish adaptability of peripheral circulation in arthritic men is the result, not the cause of the disease. Many "normal" women and most of the women with atrophic arthritis studied exhibited poor adaptability, i.e., a poor vascular response to the contrast baths. The preëxistence of an inherent vascular defect or poor adaptability may increase one's susceptibility to atrophic arthritis or may favor a graver form of the disease, but it is not the primary cause of the disease in either sex. However, the greater incidence of vascular deficiency in women may account for the greater incidence of severe atrophic arthritis in that sex. Woodmansey, Collins and Ernst were unable to distinguish so-called primary rheumatoid arthritis from "infective arthritis" by these reactions. They suggested that "primary rheumatoid arthritis" is not a different disease but is merely rheumatoid (i.e., infective) arthritis in a female who already possessed a constitutional vascular defect (sluggish peripheral vascular reaction). Disease brings the preëxisting vascular failure into greater prominence.

[This is a useful, practical piece of research, undramatic but clear and concise, and typical of the kind of research in physical medicine of which much more is needed.

Krusen at The Mayo Clinic has corroborated this work in part. Many arthritic patients responded less satisfactorily to the one minute—one minute technic than to longer alternating periods. But his preliminary observations seem perhaps to indicate differences in the vascular responses of Americans and the English (which tourists have long suspected!). His normals and arthritics exhibited optimal adaptability to either a four minute hot, one minute cold, or to a four minute hot, two minute cold regimen.—Ed.]

Ultraviolet irradiation was strongly approved<sup>64, 273, 274</sup> and considered by some<sup>450</sup> more useful and "curative" than infra-red rays. Contraindications to heliotherapy are febrile arthritis, the appearance of general or local reactions, and the coincidental presence of active tuberculosis, myocarditis or general debility.<sup>952</sup> The supposed "specificity" of short-wave diathermy and its superiority over long-wave (ordinary) diathermy were argued by several<sup>172, 173, 230, 731, 894</sup> but denied by others<sup>445, 447, 448, 553, 734, 943, 1018</sup> who found no effect from short waves except the heat. But it was agreed that it was a most effective form of deep heating and gives results not readily obtained by other forms of heat; e.g., after 20 minutes application of short-wave diathermy to a hip joint the temperature of urine was 101° F. It produces a deeper, more uniform heat and is more readily applied, but the dosage is more difficult to control.<sup>553</sup> Studies in vivo showed that it produced more heat in muscles than in bone marrow<sup>734</sup>; it produced in vitro temperatures hotter in fat than in other tissues.<sup>943</sup> Galvanic and sinusoidal currents are useful in preventing muscle atrophy.<sup>444, 877, 918</sup>

Paraffin baths (wax at 130° F.) and mud packs (at 110 to 125° F.) can be given so hot because of the low conductivity of their heat.<sup>755, 993</sup> When not overdone their dehydrating effect is soothing, but patients may overestimate their value.<sup>683</sup> The various forms, rationale and physiologic effects of hydrotherapy were described.<sup>19, 42, 211, 463, 881, 954</sup> Described also were the optimal technic for hot and cold baths (Holmes; Pennington), the value of hot-water fomentations (Phillips) and of foam baths ("useful for fat arthritics" according to Hill), an improved type of Hubbard tank for underwater therapy (Currence), an inexpensive homemade whirlpool bath suitable for arms and legs (Boynton). Brine baths may stimulate circulation through some osmotic effect on skin; they are useful in chronic, but not in subacute, atrophic arthritis (Neligan). The deep or reclining immersion bath in conjunction with undercurrent douching or manipulative exercises is most useful in quiescent atrophic arthritis, according to Copeman<sup>211</sup> and Thomson,<sup>954</sup> but should not be used in any case of infective or true rheumatoid arthritis with the "slightest sign" of clinical activity: their skins and joints are too sensitive to it, and they may react poorly even to the mildest hydrotherapy.

The advantages of spa therapy were stressed.<sup>18, 463</sup> The waters contain no "specific" for arthritis, their medicinal ingredients are merely adjuvants; heat is the important factor plus the advantage of removing the patient from his home to a new environment.<sup>264, 756</sup> Because it is often too ex-

hausting, treatment at spas and resorts may be less desirable in active cases than the more restful services available in hospitals or sanatoriums.

A list of approved American schools for physical therapy technicians, the standards required for them,<sup>26, 228</sup> and a scheme for the organization of a physical medicine unit in a teaching hospital were published.<sup>1048</sup>

*Occupational Therapy.* This form of treatment teaches arthritic patients interesting and even profitable ways of increasing joint and muscle function and possesses marked psychologic and remedial value. It is a specialized branch of physical medicine. The scheme used by the Department of Hospitals, New York City, was described. Various methods used in occupational therapy were outlined (Copeman; Merritt). Bradford stated that, although valuable, occupational therapy should "not be trusted for specific improvement, because in his interest in creating even a basket or a rug, a patient will work within the limits of joint motion and will forget to increase these limits." A survey of approved American schools of occupational therapy was made (Council on Med. Ed. and Hosp.). An association of occupational therapists has been organized in England.<sup>718</sup>

*Roentgen-Rays, Radium.* Deep roentgen therapy was considered "invaluable" in the later stages of atrophic arthritis; reduction of pain and swelling may be accomplished (no results given). Use of thorium X was noted.<sup>532</sup> Injections of water impregnated with radon were valueless.<sup>444</sup>

*Fever Therapy.* Fever therapy was considered of some value by Snow (no details) and by Ferderber, who noted "improvement" in 11 of 28 cases classified as chronic atrophic, acute infectious, chronic infectious and rheumatoid arthritis. This therapy seemed of little value to others (no details; Thompson, Wyatt and Hicks). In Paul's 28 cases, results of treatment were "excellent" in 11 per cent, good in 43 per cent, insignificant in the rest. Others<sup>40</sup> disapproved of the usual sessions of fever, but approved the use of "mild sessions" (101° F. for one hour). No details were given.

*Sympathectomy.* Atrophic arthritis was not thought by Adson to be generally suitable for sympathectomy: "unfortunately the results are not consistent."

*Hysterectomy.* Solomons concluded that hysterectomy is indicated in a few rare cases of atrophic arthritis. He reported the case of a woman, aged 40 years, whose arthritis of some years' duration became worse after the birth of her last baby. There was some leukorrhea; menstruation was "heavy." The cervix was normal. "Therefore the major operation was decided on, and hysterectomy with double salpingo-oöphorectomy was performed." The uterus was essentially normal histologically. "The patient has been well and free from pain and deformity since operation."

[It would have been interesting to know what effect, if any, this patient's previous seven pregnancies had on her arthritis. The postpartum exacerbation of her disease was similar to that noted in the case of De Sa in which hysterectomy also was done. It is not likely that the removal of the uterus per se influenced her disease; she probably experienced the nonspecific effect which may follow any surgical procedure. —Ed.]

*Nonsurgical Orthopedic Methods.* The most important factor in preventing deformities is to reduce muscle spasms by resting the part for short periods in light splints with the joint in the optimal position.<sup>124, 160, 539, 583, 759</sup> The optimal position for each joint was listed.<sup>160</sup> "If a patient with a simple distortion of one joint is not protected, serious deformities of multiple joints will certainly follow" (Stump). Splints must be removable to permit the application of heat and some joint motion. Fisher preferred light metal splints to plaster. Casts of cellulose compound are "superior to plaster of Paris splints"; they are much thinner, lighter and less expensive (Joplin). To shoulders affected with pain and muscle spasms Kuhns applied plaster abduction splints but Capener applied adjustable metal abduction splints. Osgood stressed the importance of correct body mechanics in preventing deformities.

*Surgical Orthopedic Methods.* These aim to correct deformity, restore motion, and stabilize painful or disorganized joints. The technic of the various procedures was described (Lewin). Before submitting to them the patient's joints must have been free of active inflammation for "a long period," and he must have enough physical strength, morale and financial resources to endure the long postoperative care in the hospital and the later care (Osgood).

1. Manipulation under anesthesia. In suitable cases this may be very valuable when done by skilled hands. It may shorten treatment notably but it should never be done to actively diseased joints.<sup>317, 539, 583, 759</sup> "The watchword is gentleness." Osgood considered it "of limited usefulness."

2. Capsulotomy. This may be required to correct some knee deformities but is not likely to be successful if there is already much damage to the articular surfaces of bone.<sup>738</sup> Wilson's method (1933) was approved.<sup>759</sup>

3. Osteotomy. Of limited value, this may be used to correct an awkward deformity of hip or wrist.<sup>738</sup> Briggs described a flange osteotomy to correct deformity of the knee.

4. Arthroplasty. Different methods were described.<sup>16, 759</sup> Some confined its use to cases of bilateral ankylosis of hips.<sup>738</sup>

5. Arthrodesis. This is applied chiefly to midtarsal, subastragaloid, knee and wrist joints to convert an unstable fibrous ankylosis into a stable bony one. Other joints generally ankylose themselves.<sup>738, 759</sup>

6. Arthrotomy and lavage. Fisher<sup>317</sup> considered this valuable in subacute atrophic arthritis; he often noted a most gratifying amelioration of symptoms, sometimes complete remissions for as long as 12 to 14 years. It was approved by Savage who injected Dakin's solution, and by Broomhead who reduced chronic effusions by injecting formalin and glycerin ("Murphy's fluid") which promotes absorption by its irritant effect.

7. Synovectomy. This may be valuable in certain cases<sup>317</sup> but its use in atrophic arthritis is limited.<sup>160, 759</sup> In the type in which proliferation is confined to the synovia "it is reasonable to expect the greatest benefit from synovectomy" (Swett). But synovectomy is useless if proliferation has

progressed to the extent of severe cartilaginous ulceration and absorption, as shown in roentgenograms by a material reduction in the joint space. Inge performed synovectomy in 26 knees affected by atrophic arthritis. The response was poor. Improvement was symptomatic in 61 per cent, but functional in only 34 per cent. The rest either had recurrences or were "made worse by the operation."

8. Bone puncture or drilling; forage. This procedure (Mackenzie, 1931) was done by Kersley *under local anesthesia* in 11 cases: in five "immediate local improvement" occurred which was maintained in four. One patient who was improving before operation had general improvement. The local improvement probably resulted from the enforced rest rather than the bone drilling, as comparable results were obtained by temporary immobilization in plaster alone. [Mackenzie did his operations under general anesthesia: this may account for his better results which may have represented a nonspecific post-operative effect.—Ed.] Apparently unaware of the work of Noble Smith (1890), of Mackenzie (1931 et seq.) or of Graber-Duvernay (1932 et seq.), Hipps reported bone drilling for "acute infectious arthritis" as a "new procedure." Sixteen cases of "acute monarticular inflammation" were treated: results were "excellent" in seven, good in two, fair in four, poor in three. Smears and cultures were made of the serosanguineous exudate exuding from the bone drills: streptococci, generally nonhemolytic, occasionally hemolytic, were recovered in seven cases. It was suggested that acute arthritis starts as a primary osteitis of epiphyseal bone.

[Case histories were not given.—Ed.]

*Psychotherapy.* Kindersley commented on the marked cheerfulness of arthritic patients: "It seems to be a provision of Providence that this faculty is strengthened." However, these patients need frequent sympathetic discussions that they may be helped to face their future aright, and their physicians must practice simple but sound psychotherapy.<sup>686</sup> Much can be done by the physician who is also a friend, expressing a real human interest in the patient as a person.<sup>40</sup> When these patients develop a vital faith and a philosophy of living "fear goes, improved health follows, and most important of all for the future welfare of the patient, personality changes take place" (Swaim and Harris).

*Prognosis; End Results.* Since the viscera or vital organs rarely become affected the disease rarely shortens life though it may deprive the patient of much that lends value to life.<sup>212</sup> As to the prognosis in "typical rheumatoid arthritis" Stone was very pessimistic. "About one patient in ten has spontaneous remissions, to be followed sooner or later by exacerbation; spontaneous arrest may occur at any stage, but it is very uncommon before irreparable damage has been done." According to others, however, the disease frequently becomes "arrested" or "cured." The results of a composite program of treatment in one series of cases (Thompson, Wyatt, Hicks) were as follows: of 273 patients treated for 4.5 to 8 months, on discharge 24 per cent showed little or no improvement, 34 per cent were mode-

rately improved and 42 per cent were markedly improved. One to six years later, follow-up reports on 87 of the 210 benefited patients were made: nine were worse, 18 were the same as on discharge, 30 were better, 28 were well and two were dead; in other words nearly all continued to improve after discharge. Death occasionally occurs, seldom during the acute stage but from gradual "failure," in conjunction with acute depression and progressive anemia (Copeman).

#### STILL'S DISEASE: STILL'S, CHAUFFARD'S, OR FELTY'S SYNDROME

*Clinical Data.* In two instructive papers Portis and Schlesinger reviewed the clinical and pathologic features of this disease. These include a chronic polyarthritis which may begin acutely or insidiously. In milder cases it affects chiefly periarticular tissues but in more severe cases, like chronic progressive atrophic arthritis, it affects intra-articular tissues. Periods of septic or of mild intermittent fever, enlargement of lymph nodes, generally of spleen, and frequently of liver also, occasionally pleurisy, pericarditis and subcutaneous nodules, anemia, leukocytosis in the early stages and later sometimes leukopenia with relative lymphocytosis occur. According to Findlay<sup>309</sup> Still's disease is not a special type of atrophic arthritis confined to childhood; exactly the same picture occurs at all ages. Several new cases were described in detail: two fatal juvenile cases with necropsy data (Portis), one fatal juvenile case in which the patient had been under observation for six years,<sup>107</sup> two fatal cases of adults (Taussig), and one nonfatal case of an adult, "the first case of Still's disease reported from Australia" (Lambie).

*Pathology.* In only about 20 cases have necropsy data been reported. These were reviewed (Portis) and included lymphadenitis with hyperplasia of reticulum cells, splenic hyperplasia, passive hyperemia and fatty degeneration of liver, fibrinous adhesions of pericardium, of pleura and occasionally of peritoneum, cardiac enlargement without valvulitis or Aschoff bodies and articular changes presenting "the usual appearance of chronic proliferative arthritis at various stages" (fusiform swellings, contractures, effusions rarely, cellular infiltration of synovia, some formation of pannus, destruction of cartilage). Any joint may be affected. Portis emphasized the relative frequency of amyloidosis in spleen, liver or kidneys in his and other cases. His two patients had generalized amyloidosis and died of uremia as did some others mentioned in the literature. Other causes of death have been terminal colitis or pneumonia, melena, petechial hemorrhages and abdominal or sub-arachnoid hemorrhages. In one case<sup>107</sup> death resulted from hemolytic streptococcal mastoiditis, septic arthritis and septicemia. Necropsy revealed septic arthritis implanted on "obvious rheumatoid arthritis," and amyloidosis of spleen, liver, kidneys and adrenals.

[This patient was seen by one of us, W. B., and the case is the third case of rheumatoid arthritis in which joints previously affected became septic as a result of a complicating septicemia.—Ed.]



*Laboratory Data.* Diplococci of uncertain significance were recovered from synovial fluid in two of Schlesinger's cases. In Taussig's two fatal cases of adults hyperglobulinemia with extremely high euglobulin percentages was present. In the two cases values for total serum protein were 7.25 to 14.1 and 7.1 to 9 gm. per cent (normal 6 to 8 gm. per cent), serum albumin 1.4 to 2.4 and 2.1 to 3.9 (normal 4 to 5), serum globulin 5.6 to 11.7 and 4.3 to 5.8 (normal 1.4 to 3), euglobulin 1.7 to 3.7 and 0.8 to 2.3, pseudoglobulin 3.9 to 4.7 and 2.2 to 3.9.

Roentgenographic changes in joints differ somewhat from those of other forms of atrophic arthritis, according to Schlesinger who believed that they "could almost be described as pathognomonic of the disease." They included general decalcification, destruction of cartilage, diaphyseal overgrowth, premature ossification—"changes partly characteristic of rheumatoid arthritis and partly of osteoarthritis." A similar combination of changes was noted in Lambie's case.

*Relationship to Atrophic Arthritis.* Most English and American writers regard Still's disease as merely a variety of atrophic arthritis. The reactions in spleen, lymph nodes and heart suggested to Lambie that "in Still's disease the organisms supposedly responsible for the condition more frequently enter the blood and tissues than in the common forms of chronic rheumatoid arthritis." But in his case the blood was consistently sterile. Schlesinger regarded Still's disease as a "special clinical type of rheumatoid arthritis" which, for the sake of study at present, should be distinguished from the ordinary forms. [This is our viewpoint.—Ed.] Portis favored the French view that it is a special entity. Taussig recalled that manifestations of lupus erythematosus are prolonged fever, arthritis, pleurisy, pericarditis, pneumonitis, nephritis and leukopenia; cerebral lesions may occur and later hyperglobulinemia. He suggested that cases of lupus erythematosus disseminata without cutaneous reactions may not be uncommon and that lupus erythematosus disseminata, Libman-Sack's type of endocarditis, and the Still-Chauffard's and Felty's syndromes may all be manifestations of the same disorder.

*Treatment.* Remedies recommended were general hygienic measures, physical therapy, reactions to foreign protein and orthopedic measures as for atrophic arthritis. Gold salts, successfully used by Copeman<sup>4</sup> in two cases, were not recommended by Schlesinger because severe toxic reactions frequently affected his juvenile patients so treated. The use of transfusions, liver extract, supplementary vitamins and other remedies proved valueless in one case.<sup>167</sup>

*Prognosis.* This varies notably. In some apparently hopeless cases "remarkable recoveries" occur. The active stage of the disease generally lasts about five years; the infection usually subsides with the onset of puberty. Among infants the disease may prove fatal.<sup>834</sup>

## HYPERTROPHIC ARTHRITIS

"Hypertrophic arthritis" is not a disease but a type of cartilaginous degeneration and osseous reaction to several different agents: trauma, gouty deposits, certain infections and unknown factors. The commonest form is "primary hypertrophic arthritis" which affects most elderly persons more or less spontaneously and usually involves several, but not many, joints. "Secondary hypertrophic arthritis" may affect persons of any age, and usually involves only one or a very few joints affected by acute trauma, an old infectious arthritis, chronic occupational trauma or the trauma resulting from a developmental defect of a joint. Thus the presence of osteophytes does not always indicate the presence of primary hypertrophic arthritis.<sup>763</sup>

## PRIMARY HYPERTROPHIC (SENESCENT, DEGENERATIVE, OSTEO-) ARTHRITIS

*Clinical Data.* Patients with primary hypertrophic arthritis\* react to meteorologic factors differently from those with atrophic arthritis. According to Coste and Forestier they are made worse by cold but not by dampness. In contrast to patients with atrophic arthritis, they do not feel worse at the seaside, but they too are better in dry or damp heat. Shoulder joints are affected less often by hypertrophic arthritis (in 6.6 per cent of cases) than by atrophic arthritis (in 9 per cent of cases), and less severely, according to Kuhns. Severe contractures and stiffening of shoulder joints necessitating operative procedures almost never occur in hypertrophic arthritis.

Gelatinous "synovial cysts" or "synovial lesions" develop in a few cases of Heberden's nodes over the dorsum of the fingers either between the nail and terminal phalangeal joints or between the latter and midphalangeal joints.<sup>3</sup> Similar lesions may affect persons without Heberden's nodes. Pathologic reactions in these nodes were described by Weber and Freudenthal. In the early stage rarefaction of connective tissue fibrils was seen without inflammation or formation of tumors. Later small oval cysts appeared which were lined with one to three rows of endothelial cells, filled with faintly staining fine granular masses forming a network. Older and larger cysts showed further diminution of connective tissue bundles, the space being occupied by star-shaped cells and fine fibrillary masses, the whole somewhat resembling the microscopic picture of Wharton's jelly in the umbilical cord. The nodules are sometimes painless, at other times quite painful.

[In the discussion of this report several methods of "curing" these lesions were noted: galvanocauterization, excision, incision and carbolization, cauterization with carbolic acid, and knocking or squashing them with a hammer. Radium was used unsuccessfully. In our experience many of these lesions need no special treatment as they are painless. Sometimes they recede or rupture and collapse spontaneously; occasionally they reform.—Ed.]

\* In this section "hypertrophic arthritis" refers to the primary form.

Physicians concerned with Heberden's nodes may be interested in a historical sketch of the Heberden father and son (Hale-White).

Hypertrophic arthritis of the neck will be considered in the section on hypertrophic spondylitis.

*Roentgenograms.* The roentgenographic features of hypertrophic arthritis were again described.<sup>154, 982</sup> Attention was called to the frequent presence of small "periarticular ossicles," distinctive from osteophytes, deposited in the substance of joint capsules in fingers affected with this disease (Calthrop).

Osteophytes which affect the distal phalanges are called Heberden's nodes; those which affect the proximal phalanges are called Bouchard's nodes, according to Van Dam who believed that their structures can be explained to a great extent by studying the normal structure of the skeleton. The phalanges and metacarpals have only one epiphysis, that of the former at the proximal, that of the latter at the distal end (except in the thumb, where the metacarpal epiphysis is situated at the proximal end). The bases of the phalanges are thus epiphyseal and ossified in cartilage, and the heads [are] diaphyseal and ossified from the periosteum. The marginal zone of compact bone is sharply defined at the base, but at the head merges gradually into the spongiosa. The osseous basis of Heberden's and Bouchard's nodes consists of a composite structure, a large periosteal osteophyte connected with the periosteal head of the phalanx and a pointed cartilaginous osteophyte connected with the cartilaginous base of the next phalanx.

In cases of hypertrophic arthritis terminal and proximal interphalangeal joints commonly are affected, but the metacarpophalangeal joints rarely are affected. Curiously, the base of the thumb is not uncommonly involved. In many cases the part of the greater multangular bone lying between the bases of the first and second metacarpals is disorganized and destroyed. According to Van Dam the presence of the radial artery which loops directly over this bone may be somehow responsible.

*Pathology.* The articular pathology of hypertrophic arthritis was reviewed (Ghormley). "Osteo-arthritis of the same types seen by every radiologist to-day" affected the bones of a mastodon of the Post-Pleistocene Age recently found near Charleston, N. C. (Chamberlain and Taft).

*Laboratory Data.* Studying Cooke-Arneth counts, Gibson noted significant and essentially similar shifts to the left in both atrophic and hypertrophic arthritis as compared with normals. Collins noted such shifts to the left in cases of osteo-arthritic hips with large cyst-like areas of rarefaction in articular bone. In such cases sedimentation rates, which are generally normal in osteo-arthritis, were found to be elevated. The altered rates and shifts to the left do not permit one to assume that the disease is infective in nature. The cysts were degenerative, rather than inflammatory in origin and "are not of the osteoclastomatous nature of some other bone cysts. . . . It is now clear that true osteoarthritis of the hip is quite distinct from the simple 'osteophytosis' around joints or spine, to which the term osteoarthritis should never be applied; the Arneth count may continue to prove of value in their differentiation. Experience with the Arneth count in this

disease also suggests that the count may be influenced by a local bone pathology which is quite independent of the general condition of the patient as reflected in the sedimentation rate."

*Etiology.* 1. Factor of trauma. Intricate experiments have been made to find out whether hypertrophic arthritis is a disease of usage or not. According to Van Dam, "Nature has carried out a convincing and decisive experiment on the carpo-metacarpal joints. For the carpo-metacarpal joint of the thumb is the only one of these joints which is properly mobile and at the same time the only carpo-metacarpal joint to be attacked fairly frequently by hypertrophic arthritis."

[Neither this point nor others previously noted in these Reviews have afforded convincing proof that trauma is the sole cause of primary hypertrophic arthritis. Nevertheless it is an important, perhaps the most important, predisposing and precipitating factor.—Ed.]

2. Factor of senility of articular tissues. Finn accepted the idea that the condition results from senility of cartilage: "It is a disease only if it starts early in life. . . . If we have inherited inferior cells our cartilages may give in earlier. But it seems that it is the result of the sclerosis of the blood vessels as shown in Heberden's nodes, found round the terminal joints of the fingers."

[No new data to support this idea were given.—Ed.]

3. Factor of impaired circulation. Pemberton and Scull again summarized the evidence (given in previous Reviews) which indicates that defective circulation to joints may be an important factor in the etiology of hypertrophic, as well as of atrophic, arthritis. Capillary observations made in 31 cases of symptomatic hypertrophic arthritis showed circulatory stasis in 35 per cent, intermittent flow in 32 per cent, narrowed capillaries in 75 per cent, slowed rate of flow in 28 per cent. The abnormalities were similar to, but less frequent than those seen in atrophic arthritis.

[Regardless of their importance as predisposing or aggravating factors the fact that these abnormalities are instantly present indicates that they cannot be the chief cause of the disease.—Ed.]

4. Factor of endocrine dysfunction. Some<sup>281</sup> consider the disease "endocrinal in origin" despite the fact that no known endocrine dysfunction is consistently present. Metabolic rates were above normal in 12 per cent of 116 cases, normal in 63 per cent, below normal in 25 per cent (Rawls, Ressa, Gruskin and Gordon). In this connection the work of the Silberbergs is of interest. The use of anterior pituitary implants and of acid extracts of anterior lobes of pituitary glands of cattle produced hypertrophic and degenerative changes in articular cartilages of immature guinea pigs; but the changes were "similar to those reported in human acromegaly" rather than to human hypertrophic arthritis.

5. Factor of altered metabolism. Food allergy was considered by Pottinger to be an etiologic factor in hypertrophic, as well as in atrophic ar-

thrititis. Sherwood entertained the idea that a vitamin C deficiency might aggravate hypertrophic (or atrophic) arthritis by increasing the interstitial fluid. Concentrations of vitamin C in the blood of 10 of his patients with hypertrophic arthritis varied considerably: 0.35 to 0.82 (av. 0.57) mg. per cent in five "county cases;" 0.48 to 1.6 (av. 1.0) mg. per cent in five "private cases"; average for the 10 cases was 0.76 mg. per cent. This average was considered normal by Rinehart and his colleagues who reported that "in a small series of cases of hypertrophic arthritis the plasma values [for vitamin C] were almost uniformly high."

6. Factor of infection. Polak echoed the conclusion of most workers that the disease is "certainly not of infectious origin." Nevertheless in its course definite inflammatory reactions may occur. Contrary to most investigators Hartung stated his belief that infection may incite symptoms: "While osteoarthritis is fundamentally a degenerative disease, there is little question that infection does play a part in precipitating pain."

[This idea has been supported by others also, but has not been proved.—Ed.]

*Treatment.* The great importance of reassurance was recognized. When a patient has been told that he does not have a seriously crippling or ankylosing form of arthritis "he will go home greatly improved because you have dispelled his fears" (White).<sup>1029</sup> In most cases rest and reduction of trauma, including that of obesity, are of first importance. Moore<sup>676</sup> considered the pain frequently owing to capsular stiffness, and advised patients with early osteoarthritis of hips to "keep the joint moving." He believed that despite the pain and discomfort which exercises may induce at first, increased mobility and decreased pain eventually result. [Rest has been more valuable than the deliberate use of exercises in our experience.—Ed.] The diet required is usually one with moderate caloric restrictions, especially in obese patients.<sup>135</sup> Pottenger sought to have patients avoid foods to which they were presumably allergic. The use of synthetic vitamin C seemed worth while to Sherwood. Massive doses of vitamin D were valueless (Steinberg). "It is quite useless to administer gold salts in osteo-arthritis."<sup>253</sup> Most writers<sup>531, 583, 717, 1029</sup> agreed that the removal of infected foci will not benefit joints in this disease, but may be indicated in certain cases to improve the patient's general health. However, the removal of foci seemed of importance to Hartung who believed that infection may precipitate pain. Kersley claimed to have noted improvement in some cases in which vaccines were used "in spite of the absence of rationale." Others considered vaccines valueless.<sup>422</sup>

Injections of chaulmoogra oil were given by Smith, Blocker and Tumen in 17 cases of hypertrophic arthritis: Improvement was absent in 64 per cent, "slight" in 30 per cent, "moderate" in only 6 per cent and "marked" in none. Some regarded the use of gonadotropic and thyrotropic hormones beneficial (no results given).<sup>422</sup> Others<sup>791</sup> stated that about 41 per cent of patients with mixed arthritis and osteoarthritis, especially those who were obese, "improved" following use of thyroid extract.

[One of us, F. C. H.,<sup>404</sup> has approved the experimental use of estrogenic hormones in cases of hypertrophic arthritis with menopausal symptoms. But most of us consider that endocrine therapy has not yet been proved to be of value in this disease. The effect of thyroid extract is chiefly, if not wholly, a weight-reducing one.—Ed.]

Roentgen therapy to provide relief of pain was approved (no results given) (Broomhead). Fever therapy also was not recommended.<sup>885</sup> Mecholyl iontophoresis seemed useful to some,<sup>114</sup> but it was considered inferior to the use of converse heat by Licht who used six different types of physical therapy for 68 patients with osteo-arthritis. "Relief" was afforded to 25 per cent, "improvement" to 35 per cent, no benefit to 40 per cent. The beneficial effects of various forms of hydrotherapy were stressed.<sup>211, 683, 954</sup> Thomson favored the use of warm immersion baths with hot undercurrent douches or local hot packs to relieve pain and muscle spasms in early cases, massage with douches or hot packs in more chronic cases. Brine baths were recommended by Neligan, Fango treatments by others.<sup>993</sup> Currence considered his results with underwater treatment very satisfactory, "occasionally spectacular."

In some cases Tarsey obtained significant relief of pain by peri-articular and intra-articular injections of 1 per cent procaine hydrochloride. A curious method of treatment was used by Woolf in cases of hypertrophic arthritis of knees and "intractable pain." The method consisted of injection into the affected knee joint of the patient's own fat, excised from the thigh or abdominal wall, then liquefied and converted into oil to act as an articular lubricant. Thirty injections were given to 24 patients: 16 injections were called "successes," 7 were "failures," 3 were of doubtful value, 4 produced immediate relief of pain but the patients were lost sight of. No attempt was made to explain the results. Hips were found to be unsuitable for this therapy. The disadvantages of the method were recognized by Woolf who reserved it for use only in cases quite unrelieved by the usual remedies.

Orthopedic manipulation of certain osteo-arthritic joints under anesthesia was approved by some,<sup>124, 676, 759</sup> but considered valueless, at times harmful, by others.<sup>738, 954</sup> In this disease bits of cartilage or bone may become detached and form "joint mice": If they produce pain or instability they may require removal, but under other circumstances cheilotomy or the removal of chondro-osseous overgrowths has given disappointing results (Broomhead; Osgood). Platt stated that despite the technical simplicity of bone puncture or forage (drilling of the femoral head) the operation "has failed to become popular in the orthopaedic clinics of Great Britain and the United States. It would seem to be an empirical procedure and likely to be of transitory value only." [No results were reported.—Ed.] Subtrochanteric osteotomy and acetabuloplasty are reputedly indicated in selected cases (Platt). But arthrodesis of painful hips was considered by Osgood to be useful in more cases than reconstruction operations. Watson-Jones considered the use of a Smith-Petersen nail of value in performing arthrodesis. Since the synovial

changes that occur in this disease are relatively unimportant secondary effects, Swett considered synovectomy in general inappropriate. Inge also considered it theoretically contraindicated but he performed it on 20 "painful and disorganized" knees of 13 patients: 70 per cent were "improved anatomically," 90 per cent were "improved symptomatically," 60 per cent were "improved functionally. . . . Some of the most satisfactory and even dramatic results were seen in elderly patients with osteo-arthritis, several of whom were released from bed or wheel chair and restored to relatively active lives."

### SECONDARY HYPERTROPHIC ARTHRITIS

In most cases of tarsometatarsophalangeal exostoses there is a definite history of trauma from blows or strains or from the continual pressure of ill-fitting footwear. Moore and Ashby accepted the theory that the actual provocative factor causes a rupture either of the periosteum, as it enters its point of insertion, or of its tendinous insertion. In the later stages of hallux valgus or hallux rigidus the compensatory changes of traumatic osteo-arthritis (secondary hypertrophic arthritis) appear. Much can be accomplished by conservative measures: padding, strapping and the use of proper shoes, graded exercises for flat feet and weak muscles. Surgical correction of bunions and excision of exostoses is often required and gives relief.<sup>250, 678</sup>

### BACKACHE AND SCIATICA

*General Remarks on the Causes of Backache and Sciatica.* Many short general articles on this topic appeared which described the multiple causes of backache and sciatica, the need for a detailed and rather specialized history and physical examination in every case, the use of the various physical tests and maneuvers, and roentgenologic examinations which should be made.<sup>113, 138, 153, 286, 476, 493, 494, 685, 821</sup> Despite the real contributions recently made to this subject it is still a very confusing one. Several classifications of the causes of backache and sciatica were presented,<sup>113, 271, 286, 509, 742</sup> but it is difficult after reviewing current literature to form an opinion on the relative frequency of the various causes of backache. According to Epstein 90 per cent of low back pain is due to postural defects; according to Wildman 75 per cent of backaches of men and 50 per cent of those of women are due respectively to genito-urinary and gynecologic conditions. But Raddin concluded that retroflexed and retroverted uteri rarely cause backache. According to Bankart the commonest cause of persistent low back pain is sacroiliac strain. The commonest cause of sciatica was stated to be spinal osteo-arthritis by Echols, chronic fatigue of leg and lumbar muscles by Lindstedt, "rheumatism" by Slot, and ruptured intervertebral disk by Jaeger. In contrast several writers (Love, Adson and Craig; Poppen) considered the last to be the cause of only a small percentage of cases of sciatica. This confusion as to the relative importance of the various lesions that may produce

backache and sciatica could and should be cleared away by the coördinated efforts of several specialists. It would simplify the problem for the general practitioner, who is inclined to believe that too many specialists (urologic, gynecologic, orthopedic) jump to the conclusion that almost every backache pertains to his particular specialty.<sup>286</sup> [But no two or more specialists will ever agree on the cause of a backache.—Ed.] Of 417 cases of low back pain encountered by Steindler atrophic or hypertrophic arthritis was assigned to be the cause in 142, "posterior ligamentous syndrome" in 114, "myofascial syndrome" in 104, and anomalies of lumbar vertebrae in 57 cases. Steindler described a test made by injecting procaine hydrochloride to determine in a given case whether root pain is due to reflex or to compression of the root.

*Backache from Urologic Lesions.* Many low backaches are due, according to Wesson, to referred pain from prostatitis, to myofascitis or arthritis secondary to prostatitis which is more often nonspecific than gonococcal. He recommended urologic examinations in cases of low back pain unrelieved after a few days of conservative medical and orthopedic care.

"Suprarenal backache" noted by Hoffeld, was presumably characterized by pain over the renal region or higher, generalized weakness, fatigue and sometimes by a low sodium chloride content of blood. In one case backache was provoked by feeding foods rich in potassium.

[This report is not convincing. No pathologic or biochemical data were given.—Ed.]

*Backache from Gynecologic Lesions.* Backache from cervicitis was described (Raddin). Features were sacral pain with "distress" in either or both lower abdominal quadrants, extension of pain down the front or back of legs, and vaginal discharge. Pain is relieved when the patient lies down, is worse when the patient is ambulatory, and is markedly aggravated by stooping, straining at the stool, or lifting.

*Backache from Gastrointestinal Disease.* A few cases of backache apparently definitely caused by peptic, duodenal or jejunal ulcers were described (Compere, Jones,<sup>501</sup> Mixter). In four of Mixter's seven cases of mid-dorsal backache caused by duodenal ulcer (one of which was in himself) gastrointestinal symptoms were long absent. Visceral disease (bronchiectasis was also mentioned) may cause backache, but examples were cited in which spinal lesions (fractures, extradural cysts, giant-cell tumor, tuberculosis) induced abdominal pain, sometimes simulating appendicitis.<sup>206</sup>

*Postural Backache.* This is a common,<sup>118</sup> some say<sup>286</sup> the most common, type of backache and is related to poor posture, flat feet, scoliosis, round shoulders, large abdomen, knock knees and other conditions which shift the body's center of gravity and provoke strain in the lumbar muscles and those used in walking. It is sometimes related to the use of high-heeled or ill-fitting shoes.<sup>742</sup> The low back pain may be associated with sciatica<sup>579</sup> and is usually "static," relieved by rest and recumbency, aggravated by activity and worse at the end of the day. The sequence of events includes muscle weakness, imbalance and contracture. These are evidenced by an increased



lumbar curve, pelvic asymmetry, slight adduction and internal rotation of an affected hip, tension on gluteal muscles, abductors of the hip, the piriformis and on fascia lata of the gluteus maximus. Tension on the sciatic nerve is thus produced (Lenhart and Kendall). Postural sciatica, according to Lindstedt, does not result from local mechanical conditions alone but from the operation of them in persons with a "constitutional neurosis" or general hypersensitivity to pain. The condition is treated by heat, postural exercises, swimming, reduction of weight in obese cases, the part-time use of corset or other support for the back, a  $\frac{1}{4}$  to  $\frac{7}{8}$  inch lift to the heel of the shoe on the unaffected leg to shift the pelvis and abduct the affected hip, and other shoe corrections to rotate the leg externally.

*Backache from "Functional Decompensation."* Functional decompensation of the back was again<sup>5</sup> defined by Hauser as an imbalance between the capacity of the back and the load of work demanded of it. It may be part of a general condition of weakness and fatigue, and results in inflammation at the lumbosacral and sacro-iliac joints. Present are low back pain, increased spinal curves, general and local fatigue. Treatment includes rest in bed or adhesive strapping, exercise to increase the muscular capacity of the back, and if necessary, the correction of postural deformities by application of a cast.

[This condition seems vague. Its symptoms and signs simulate those of more established conditions. Is it not merely a form of postural backache or chronic lumbosacral strain?—Ed.]

*"Lumbosacral and Sacro-Iliac Backache or Strain."* This is a poorly defined syndrome because it undoubtedly represents not one but many different conditions. Sacro-iliac or lumbosacral backaches may arise insidiously or appear suddenly as when a person stoops to lift something, gets a sudden severe pain in the back and thereafter can rise or move only with the greatest pain and difficulty. This generally is called "lumbosacral or sacro-iliac strain" but there is no agreement on what lesion or lesions are actually responsible for the disability. Some consider a true strain or sprain responsible, microscopic tears in muscles or ligaments near the joints (Bankart, Pusitz); others blame the condition on a slight subluxation of the sacro-iliac joint (Ryan). There is no such thing as "sacro-iliac strain" according to Forrester who conceived the lesion to be a tear or stretching of soft tissues, muscles or tendons, and not a lesion of the joint itself. Some writers regard the pain as due to a "fasciitis" or "spinal fibrositis." The signs of fascial contracture were listed by Kendrick as stiffness in the lower part of the back and limitation in flexion when the knee is held extended, a positive Ober's sign, and a positive Ely's sign. Gratz concluded that the fascial planes of the human body function like joints. As a result of trauma and inflammation, fascial adhesions and "myosynovitis" involve these planes. These may produce chronic radicular muscular pain. Incident to some sudden motion these fascial adhesions may tear and produce acute

symptoms. Gratz made "pneumofasciograms" by injecting air into fascial planes; the air was distributed evenly in normals, unevenly in many arthritics and in many patients with low backache. Others believed that the use of the term "fasciitis" to explain these cases of chronic or acute low backache may not be correct since the examination of removed fascia has failed to reveal any abnormality (Harbin).

As a background for his study of "sacro-iliac joint pain" Gray made a detailed study of the finer anatomy of the sacro-iliac joints. Detailed measurements were made of the size and position of the joints and related bones; new observations, some at variance with those commonly reported, were made on pelvic inclination, mobility and axes of rotation. As a result of clinical studies Gray concluded that in cases of acute and chronic sacro-iliac pain lumbar and sacral joints are "not subluxated nor slipped but rather roughened by infection and impacted or locked at one extreme of the normal slight but real motion." In some cases of unilateral sacro-iliac pain the disease is in the lumbosacral, not the sacro-iliac joint according to Goodwyn. Straight leg raising is limited in sacro-iliac, but not in lumbosacral, lesions; flexion of lumbar portion of the spine is limited in lumbosacral, but not in sacro-iliac disease (Breck). In cases of arthritis both regions can be affected.

The treatment recommended for "lumbosacral and sacro-iliac strain or backache" was similar. For acute sacro-iliac strain Barry used injections of procaine hydrochloride to relieve acute muscle spasm; then a plaster cast for 10 days, in order that the patient may work, then a sacro-iliac belt. For both lumbosacral and sacro-iliac strain Breck advised in acute cases complete rest on a hard bed, the use of a lumbar pad, heat, strapping or a belt; casts were rarely necessary but in severe cases traction was used. For chronic cases he advised limited activity, heat, the removal of infected foci, the use of a belt, epidural injections, roentgen therapy, manipulations occasionally and if necessary a fusion operation. Gratz stated that insufflation of air may free fascial adhesions in some of these cases. Results from this treatment were satisfactory in 23 of 45 cases. According to Littlejohn rest can be overdone and in recent cases he prescribed exercises, manipulation without use of anesthesia, but if necessary with anesthesia, and fusion if no relief was noted otherwise. For sacro-iliac strain manipulation was recommended strongly by others also.<sup>47, 363, 384, 507, 508, 528, 783, 820</sup>

The strongest argument on behalf of manipulation was made by Gray who quoted Sir Robert Jones (1931) thus: "Forcible manipulation is a branch of surgery that from time immemorial has been neglected by our profession, and, as a direct consequence, much of it has fallen into the hands of the unqualified practitioner. Let there be no mistake; this has seriously undermined the public confidence, which has on occasion amounted to open hostility. If we honestly face the facts, this attitude should cause us no surprise. No excuse will avail us when a stiff joint which has been treated for many months by various surgeons and practitioners without effect, rapidly regains its mobility and function at the hands of an irregular practitioner. We should be self-critical, and ask why we missed such an opportunity ourselves. The problem is not

solved by pointing out mistakes made by the unqualified—the question at issue is their success. Reputations are not made in any walk of life simply by failures. Failures are common to us all, and it is a far wiser and more dignified attitude on our part to improve our armamentarium than dwell upon the mistakes made by others." Gray also quoted Paget (1867): "Learn then to imitate what is good and avoid what is bad in the practice of bone-setters." Gray described with photographs methods of manipulation, some to be used without, others with anesthesia, the former being considered safer. Mennel's methods (1938) were used by Pusitz.

Using manipulative methods without anesthesia Joster obtained "gratifying recovery" in a high percentage of cases of acute and chronic low back sprain, fasciitis, postural backache and apophyseal dislocation. Gilcreest described the manipulative methods (used with and without anesthesia) whereby he obtained "rapid and permanent cures" in most cases of lumbosacral and sacro-iliac strain. Bankart considered manipulation under anesthesia effective in 90 per cent of cases of sacro-iliac strain: arthrodesis will cure the rest. But for cases of lumbosacral strain he considered manipulation, supports and exercises of no value. According to him ligaments cannot be stretched but can be divided surgically: results therefrom were "entirely satisfactory" in almost every case. But a strong note of warning was sounded by Selig who reported a case of paraplegia from a hemorrhage following manipulation for sciatica; recovery was slow and incomplete. In many cases of low back pain and sciatica the indications for certain forms of treatment are often not clear; this is particularly true of manipulation which Selig regarded as drastic, hazardous and unjustified by the present state of our knowledge.

*Backache from Tight Fascia Lata and Iliotibial Band.* Ober again discussed his conception that in certain cases sacro-iliac pain and sciatica arise from contracted fasciae of the thigh and spastic iliotibial bands. He again recommended fasciotomy for selected cases as a procedure which will relieve 75 per cent of patients treated. The operation was considered useful by Barry. It was used by Smith<sup>878</sup> in cases of low back pain with, but not in those without, sciatica, by Pusitz only in cases in which abduction contracture was present and then only as an adjunct to other methods. Harbin also used it despite the fact that examinations of presumably affected fascia revealed no pathologic change.

*Relation of the Piriformis Muscle to Sacro-Iliac Backache and Sciatica.* The sciatic nerve usually emerges from the pelvis by passing beneath the piriformis muscle. But the muscle may split into two separate heads: the nerve also may divide within the pelvis into its tibial and common peroneal portions. Thus six anatomic relationships are possible, five of them being "abnormal." Some anatomists have reported the presence of an abnormal relationship in from 3 to 35 per cent, generally from 10 to 15 per cent of cadavers. Beaton and Anson found an abnormal relationship of the sciatic nerve to the piriformis muscle in 10 per cent of 240 specimens examined. When such an abnormality exists, sciatic pain may be produced if chronic in-

inflammation of the piriformis muscle is present and spasm of the inflamed muscle compresses the nerve or its divisions passing between the heads of a divided muscle, or similar results may follow mere stretching of the nerve where it leaves the pelvis superior to the undivided muscle.

*Diseases of Intervertebral Disks.* Two main pathologic conditions affect intervertebral disks: (1) senile fragmentation and thinning, related perhaps to long continued trauma but not to acute trauma, and (2) ruptured disk with herniation of nucleus pulposus and other material; this generally occurs earlier in life than the first condition and is usually related to acute trauma.

1. Senile fragmentation of disk. In later life fragmentation of the cartilage plate may occur; granulation tissue may invade the disk from adjacent vertebral bodies and replace the nucleus pulposus so that the disk becomes merely fibrous tissue or even bone. As a result the vertebral bodies come closer together. In the thoracic and upper part of the lumbar regions kyphosis generally results. In the cervical and lower dorsal regions apophyseal subluxation generally occurs with distortion and constriction of intervertebral foramina, or in extreme cases with painful impingement of the tip of the articular process against the pedicle above or the lamina below. Hadley gave roentgenographic examples of these conditions. Symptoms produced are pain, tenderness, muscle spasm, limited motion, radiculitis, sometimes disturbances of reflexes, muscle atrophy and root pain which is aggravated by coughing or sneezing.<sup>187</sup>

2. Ruptured intervertebral disk; herniated nucleus pulposus. The clinical and laboratory features of this condition and methods for its diagnosis were again reviewed in a score of papers concerned with over 200 new cases proved at operation.<sup>51, 67, 263, 304, 305, 323, 340, 375, 416, 491, 529, 556, 597, 598, 599, 600, 673,</sup>

<sup>687, 764, 856, 998, 1051</sup> Particularly noteworthy were the papers of Barr, Bell and Spurling, Fincher and Walker, Poppen, and Love and Walsh.

*Etiology.* A history of trauma, such as that from lifting a heavy object, a fall, a twisting strain, or rarely that from lumbar puncture needle, was present in 50 per cent of the cases of Fincher and Walker, in 80 per cent of Barr's cases, in 71 per cent of the cases of Love and Walsh. Symptoms may appear rather suddenly after the injury (as they did in 32 per cent of Love and Walsh's cases, in 50 per cent of Barr's cases), or they may appear insidiously or suddenly some time after injury (as they did in 30 per cent of Barr's cases, in 39 per cent of those of Love and Walsh). No history of injury was present in 29 per cent of Love and Walsh's cases, in 20 per cent of Barr's cases, in 50 per cent of Fincher and Walker's.

*Site of lesion.* Almost any intervertebral disk may be involved but in most cases the lower lumbar disks are affected.<sup>304, 305</sup> In all of Barr's 58 cases lumbar or sacral disks were affected, the fourth lumbar disk in 50 per cent, the fifth in 35 per cent, sacral disk in 15 per cent. In the 100 cases of Love and Walsh 113 protruded disks were removed. A single disk was producing symptoms in 88 cases (6 cervical, 6 thoracic and 76 lumbar disks); in 12 cases more than one disk, generally lumbar, was

affected. Of the total protrusions 35 per cent affected the fourth lumbar, 42 per cent the fifth lumbar, 9 per cent the third lumbar disk (a total of 85 per cent); other lumbar disks and the thoracic and cervical disks were affected in less than five cases each. Among Poppen's 26 cases protrusions were at the fourth lumbar disk in 22, at the fifth lumbar disk in two, at more than one disk in two cases.

**Symptoms.** In Love and Walsh's cases of protrusion of cervical or thoracic disks a history of injury was often indefinite; in some cases pain was slight but neurologic signs and symptoms of extradural compression were present. In cases of protruded lumbar disks there was a history of injury at the onset of symptoms in 34 per cent, no history of injury in 27 per cent, and a history of injury some considerable time before symptoms in the rest. Symptoms were generally "constant and characteristic" and resulted from impingement of protruded disk material on one or more spinal nerve roots, generally of the cauda equina, the roots of which form the lumbosacral plexus.<sup>51</sup> The sex incidence was almost identical in the series of Barr (males 75 per cent, females 25 per cent) and of Love and Walsh (males 77 per cent, females 23 per cent).

In most cases the patient complains of low back pain, occasionally without, but almost always (in 92 per cent of cases)<sup>600</sup> associated with sciatica. Indeed sciatica is such a dominant symptom that some writers now consider the majority of cases of sciatica to be caused by ruptured disks.<sup>491</sup> Herniated disks were the cause in 24 of 31 consecutive cases of low back pain with sciatica in which Fincher and Walker made lipiodol studies. Others<sup>599, 764</sup> insist that only a small percentage of cases of sciatica are caused by ruptured disks and Barr warned of the untempered enthusiasm of those who assume that this entity is the cause of all sciatica. Nevertheless it is an important and common cause of sciatica and should be thought of in all chronic cases.

Sciatica was unilateral in 80 per cent, bilateral in 20 per cent of Barr's cases, unilateral in 77 per cent, bilateral in 23 per cent of the cases of Love and Walsh in which sciatica was present. Additional symptoms and signs included local lumbar tenderness (in 50 per cent), root pain on coughing or sneezing or on jugular compression (in 39 and 40 per cent), kyphos or flat back (90 per cent), sciatic scoliosis (60 per cent), positive Lasègue's sign or limitation of ability to raise the extended leg (in 82 and 100 per cent), ankle jerk absent or reduced (in 50 and 57 per cent), sensory changes consisting of anesthesia or hyperesthesia (in 35 and 49 per cent), motor changes consisting of muscle weakness or paralysis (in 15 and 26 per cent), sphincter disturbances (in 5 and 8 per cent): the percentages were those noted by Barr, and by Love and Walsh. In some cases neurologic signs were absent; in many cases the only signs were sciatica and reduced Achilles reflex. Symptoms were constant in 60 per cent of Barr's cases but in only 14 per cent of those of Love and Walsh; they were intermittent in 40 and 86 per cent of these cases respectively. The intermittency of symptoms probably is due to the fact that some protrusions are restored partially and temporarily and later the material extrudes again. It has been noted that

kyphotic flexion of the spine of cadavers caused a return of protruded disks into almost normal position.<sup>600</sup>

**Diagnosis.** Obviously the condition presents no classic picture; its symptoms resemble those of sacro-iliac and lumbosacral strain or of thickened ligamenta flava. Ordinary roentgenograms are of little value in diagnosis. Many persons have narrowed intervertebral spaces which are not associated with clinical signs and symptoms; in cases of ruptured disks producing pain, narrowed intervertebral spaces are not always present.<sup>67</sup> To make a presumptive preoperative diagnosis of ruptured disk, examination of spinal fluid and spinograms made after injection of air or lipiodol are required. Since most of the protrusions are low in the spine, spinal puncture should be as low as possible, preferably at the lumbosacral interspace<sup>51, 764</sup> or at the second or third lumbar interspace.<sup>598</sup> The value of total protein in spinal fluid was over 40 mg. per cent in about 75 per cent,<sup>598</sup> about 80 per cent<sup>529</sup> and 85 per cent<sup>51</sup> of cases in the series reported. In Love and Walsh's cases of cervical and thoracic protrusions it was 40 mg. in 29 per cent, more than 40 mg. in 71 per cent; in 80 per cent of their cases of lumbar protrusions it was 40 mg. or more (up to 240 mg.).

If the spinal fluid protein is more than 40 mg. per cent (or sometimes even if it is normal but severe protracted sciatica is present)<sup>764</sup> a spinogram should be made. Formerly lipiodol was used routinely but because lipiodol occasionally produces irritating symptoms if not removed, it is now recommended that lipiodol be used with considerable discretion.<sup>375</sup> Since 90 to 95 per cent of patients with sciatica recover spontaneously or on conservative treatment patients with sciatica should not be subjected routinely to a highly technical and possibly irritating lipiodol spinogram (Barr). Some preferred spinograms made by injecting air (Poppen); most defects are revealed by "pneumospinograms"; the air is innocuous and disappears rapidly. Others<sup>509</sup> considered the reversed Queckenstedt test useful in cases strongly suggestive of ruptured disk but in which protein in the spinal fluid is normal. When lipiodol is used most investigators injected 4 to 5 c.c.<sup>51, 529, 600, 687, 764</sup> Harbin used 3 c.c. According to Bell and Spurling 2 c.c. are sufficient and entirely harmless in their 10 years' experience; this amount gave them better visualization than larger amounts which were considered unnecessary and possibly harmful. But others<sup>566, 1051</sup> considered the use of 5 c.c. necessary; 2 c.c. may fail to reveal defects produced by slight protrusions. Mild reactions to unremoved lipiodol were occasionally noted: temporary retention of urine, slight fever and pain; hence the use of such spinograms entails a slight risk but one which is "without any real danger."<sup>1051</sup> Fincher and Walker noted no reactions in their 31 cases and cited the experiments of Globus (1937) in which no neurologic residues and no encysted lipiodol were seen. Lipiodol may occasionally become encysted in cases in which inflammatory conditions have preceded its use.<sup>764</sup> Hence lipiodol should not be used in the presence of suspected inflammatory lesions; it should never be injected at temperatures above that of the body; it should not be used if it is cloudy.<sup>600</sup> Spinograms were made after injection of lipiodol by Echols only in cases of sciatica unresponsive to the usual medical and orthopedic measures, by Barr only in cases of intractable or recurrent sciatica with neurologic changes owing to pressure on a nerve root, by Poppen only in suspected cases of protrusion in which spinograms after injection of air were inconclusive. The technic of making spinograms and their interpretation were described in detail.<sup>67, 566, 1051</sup> The filling defects produced by the ruptured disks are visible in over 90 per cent of cases according to Barr; but since normal nerve root sleeves fill with great variability the presence of an abnormal shadow of a root sleeve in a roentgenogram should not be considered too significant unless neurologic examination indicates disease at the same level.<sup>67</sup> Very occasional false positive defects are revealed by spinograms: in two such cases Poppen at operation found only chronic thickening of the arachnoid.

Treatment. Laminectomy and removal of the protruded disk material were successful in practically all the reported cases. Relief was obtained in all of the 24 cases of Fincher and Walker, in the four cases of Kendrick and Bunts, and in 24 of Poppen's 26 cases. Of Barr's 58 patients so treated, 54 were "well or markedly improved"; three were unimproved; there was one postoperative death. In their series of 100 cases Love and Walsh reported relief and no recurrences in 99 cases, and one postoperative death; an additional 100 laminectomies were later done without a death.<sup>598</sup> In Love's first series of 100 cases (Love and Walsh) there were no recurrences of pain, but in one of the next 50 surgical cases, pain returned two months after operation. A second operation was performed and complete relief was obtained without a later recurrence. At the first operation probably only part of the fragmented disk protruded; more protruded later.

The question of whether the spine should be fused at the region of laminectomy is unsettled. If articular facets were left intact Barr considered fusion unnecessary, otherwise he favored it to prevent symptoms of a weak back. Love and his colleagues preserved the facets and found fusion unnecessary in 150 cases. In many cases the protruded disks were associated with thickened ligamenta flava; these were resected.<sup>67, 600</sup> Jaeger noted that sometimes the cartilage was injured so far laterally that no filling defect was visible in spinograms; cartilage fragments pressed on the caudal roots, not inside the dura, but as they passed through intervertebral foramina. In such cases pain was relieved by bilateral rhizotomy of the sensory root.

*Symptoms Caused by Narrowed Intervertebral Foramina.* When apophyseal subluxation occurs either as a result of senile fragmentation or of traumatic rupture of intervertebral disks, intervertebral foramina are encroached on by masses of connective tissue from the posterior joint capsule and the disk margin or by bony exostoses. As a result nerve roots are crowded and sometimes actual fibrosis occurs (Hadley). Turner discussed his study (previously reported with Oppenheimer,<sup>4, 5</sup>) of 70 cases of narrowed cervical intervertebral spaces, with or without hypertrophic arthritis, but associated with diminished size of intervertebral foramina. Pains in the shoulder girdle, arms and precordium were commonly produced. Treatment was the use of repeated traction with the head and neck in a sling.<sup>4</sup>

"The Swollen Atrophic Hand." Under this title Oppenheimer described 14 cases in which unilateral narrowing of upper cervical intervertebral foramina produced swelling and atrophy of the hand on the same side. The patients complained chiefly of their hands, not of their neck. They had swelling and pain of the whole hand and wrist, a wrist alone, or of only one or two fingers. It was not confined to periarticular tissues. Redness was absent. Joints were freely movable. Sometimes there was atrophy of skin and interosseous muscles. In four of the 14 cases a degenerative reaction was present in the muscles of the affected arm. In all recurrent "rheumatic pain" in the shoulder girdle or deltoid region of the affected side, tingling sensations in finger tips, and subjective but no objective sensory disturbances

had been present for weeks or years. In some cases there were no symptoms referable to the neck. Roentgenograms revealed decalcification of the bones of the affected hands and wrists, but joint spaces were normal (unlike atrophic arthritis). Anteroposterior and lateral roentgenograms of the cervical portion of the spine did not clearly demonstrate the lesions which were shown by a special technic for oblique views of the neck. In each case there was narrowing of intervertebral foramina above or including those of the fourth cervical vertebra. Swelling and atrophy of the hand were independent of the disease producing the narrowing of the foramina. Causes of the latter were fractures of cervical vertebrae, exostosis, subluxation of vertebrae, thinning of intervertebral disks, and isolated arthritis of the cervical portion of the spine. Rarefaction of the bones of the hand occurred with swelling and atrophy of the skin but was independent of atrophy of the interosseous muscles. The condition represents a trophic disturbance caused by pressure on cervical nerve roots within the intervertebral foramina, and must be distinguished from the swellings which may accompany neuritis, scleroderma, acrodermatitis atrophicans, and atrophic arthritis.

Ultrashort wave treatments over the neck were given to seven patients: six responded almost at once, pain and swelling subsided after three or four treatments and did not recur; within several months muscles and bones became normal or almost so. No other therapy was used: decongestion of nerve sheaths may have been accomplished. The unrelieved patient refused operation, although a fractured articular process was displaced into the intervertebral foramen.

[This is an interesting report which needs verification.—Ed.]

*Backache and Sciatica from Hypertrophied Ligamenta Flava.* The close anatomic connection of this ligament, the cauda equina and sciatic nerve was described.<sup>7</sup> Presumably as the result of trauma (fall on buttocks, lifting heavy objects) in most cases (sometimes perhaps as the result of inflammation) the ligaments are stretched or partially torn (or inflamed) and heal with thickening and contracture. This produces pressure on nerve roots as they emerge from intervertebral foramina. Symptoms produced are identical with those from herniated disk; the two conditions cannot be differentiated even by spinograms. This is immaterial as the treatment of both involves laminectomy. Often both conditions coexist. Common symptoms are low back pain, chronic or intermittent, generally associated with sciatica; the Achilles reflex usually is reduced or absent. Concentration of protein in the spinal fluid is increased. Lipiodol spinograms reveal partial or complete subarachnoid block. Treatment consists of laminectomy and wide removal of the enlarged ligamentous material. Relief in 15 cases was reported (Abbott, Brown,<sup>127</sup> Flothow, Harbin). The average thickness of the normal ligament at the fourth lumbar space is 4.4 mm.; the diseased ligaments were from 11 to 30 mm. thick and were markedly fibrosed (Abbott).



*Backache from Developmental Anomalies.* Among 1000 patients with low back pain seen by Williams 29 per cent had lumbosacral anomalies, 7 per cent had sacralization, 9 per cent lumbarization, 8 per cent imperfect fusion of sacral lateral masses, 3 per cent spondylolisthesis, 2 per cent fragmentation and anomalies of facets. Williams concluded that most patients with such anomalies have localized or segmental symptoms caused by degenerative changes induced thereby, or by direct mechanical involvement of nerve roots. [Many patients with congenital spinal anomalies have no symptoms. It would have been interesting had Williams also noted the incidence of such anomalies in 1000 persons *without* low back pain.—Ed.] According to Goodwyn such anomalies may not produce pain per se but may produce pain when aggravated by injury or affected by "toxemia." Congenital anomalies of lumbar spine seemed to Clarkson and Barker to be less frequent causes of low back pain than narrowed lumbosacral joints; they reported two cases of backache owing to false articulations between large clubbed transverse processes and the sacrum. Two cases of unusual hereditary malformation of cervical and thoracic vertebrae were noted by Jarcho and Levin in a brother and sister; the condition was related to the Klippel-Feil cervical anomaly—short, rigid neck, low hair line.

*Backache from Spondylolisthesis.* Details of 583 cases of lumbar spondylolisthesis seen at The Mayo Clinic in 20 years were reported by Meyerding.

In 82 per cent of the cases there was a forward displacement of the fifth lumbar vertebra on the sacrum. Interlumbar displacement was present in the rest. Many persons have symptomless spondylolisthesis: the condition was noted in more than 10 per cent of clinic patients. But in all the 583 cases reviewed symptoms were present: backache in 63 per cent, backache and pain in legs in 17 per cent, pain in hips and legs in 8 per cent, deformity, stiffness, or paralysis in 2 per cent, miscellaneous symptoms in 10 per cent. The condition was previously diagnosed in only 7 per cent. The presence of the anomaly can be suspected on other grounds but roentgenologic diagnosis is best. A history of trauma was found in only 48 per cent. Men were affected in 70 per cent, women in 30 per cent of cases; among Williams' 32 cases sex incidence was about equal. Conservative treatment was used in 83 per cent of Meyerding's cases: in mild cases a lumbosacral corset; in more severe cases reduction of the deformity by traction and the prevention of its recurrence by the use of a cast. Surgical treatment (double massive bone graft) was necessary in only 17 per cent.

*Reverse Spondylolisthesis; Posterior Displacement of the Fifth Lumbar Vertebra on the Sacrum.* This condition was present in 4 per cent of Meyerding's cases. The condition was described by Smith (1934) who discussed it again.<sup>878</sup> Such a posterior displacement which has seemed theoretically impossible to many does occur; the displacement seldom exceeds  $\frac{1}{4}$  inch. The fifth lumbar body rests, not on the sacrum, but on the nucleus pulposus. From this position it can tip backward easily if the lateral articulations are

so constructed as to make this possible. According to Smith, in most cases of posterior displacement the articulations are of the anteroposterior or asymmetrical type. Symptoms of reverse spondylolisthesis are repeated attacks of low back pain which may be initiated suddenly by bending; pain in thigh and leg and sciatic scoliosis may occur.

*Coccydynia (Coccygodynia).* For cases of acute traumatic coccydynia Pusitz recommended manipulation, with or without anesthesia, to correct displacement and prevent adhesions. Treatments are given semi-weekly, and may be temporarily painful.

*Additional Comments on the Treatment of Backache and Sciatica.* It becomes increasingly obvious that numerous conditions may cause low back pain and sciatica. "It is as antiquated to make a diagnosis of 'sciatica' today as it is to make a diagnosis of 'headache.'" <sup>600</sup> Two forms of treatment used in selected cases of a variety of conditions producing low back pain and sciatica were injections of analgesics, and fusion operations. Epidural injections of normal saline solution were used in cases of "chronic fasciitis." <sup>528</sup> For several conditions Steel used intraneural and epidural injections of procaine hydrochloride, and paravertebral injections of alcohol. The technic was described. Epidural injections of procaine, in conjunction with manipulations, gave successful results in 75 per cent of "some four or five hundred cases of [presumably rheumatic] sciatica" encountered by Slot. Irwig considered results from eucupine oil more lasting than those from procaine.

Indications for fusion operations in cases of low back pain and sciatica were restated. <sup>271, 375, 670, 878</sup> Most physicians, as did Smith, <sup>878</sup> recommended the use of fusion operations only in cases unrelieved by conservative measures. In about 90 per cent of Smith's cases of low back pain response was satisfactory to conservative remedies; in the rest lumbosacral fusion was used; results were good in 80 per cent of those so treated. According to Eggers fusion should *not* be reserved for "resistant cases"; in most of these, benefit will not result. Fusion was recommended chiefly for patients relieved by rest, made worse with activity, again relieved by rest. Such reactions indicate the presence of some mechanical irritation. Fusion operations were performed on the middle-aged, not on the old or the young. The number of persons whose condition is suitable for fusion operation is small and insignificant compared to the total number of persons with backache. Goodwyn's views were also conservative; he noted permanent relief in only a few cases of sacro-iliac and low back pain.

*Miscellaneous Conditions of the Spine.* 1. Spinal malignancy. In such cases the constancy and severity of pain rather soon become notable features; pain is not relieved by heat, rest or splints and usually requires narcotics in time. In suspected cases roentgenograms taken from different angles and made from time to time are required for diagnosis. Pain may antedate roentgenographic evidence of metastatic malignancy by two to 12 months or more. Miltner noted complete relief of pain in 41 of 57 patients treated by

subarachnoid injections of alcohol combined with roentgen therapy (as used by Poppen, 1936). In special cases plaster jackets or body braces were used.

2. Spinal actinomycosis. One case was reported (Flynn and Gillies).

3. "Neurotic backs." This is not a wholly functional condition but represents a traumatic neurosis secondary to real injury. Patients so affected are usually worried, apprehensive of their physical examination, highly nervous but coöperative, open-minded and sincere in describing their complaints. Limited motions and muscle spasms are absent; patients are inaccurate in relocating their painful spots. The latter are usually tender only on deep pressure. Physicians should gain the patient's confidence by making roentgenograms and tests to show one's earnest desire to find any trouble. It is psychologically useful to deliberate over the final diagnosis for several days or weeks. Then a careful sincere explanation of the condition by the physician may end the neurosis (Forrester).

4. Backache of malingerers. The malingerer who claims to have been injured, often enters the office with canes or on crutches long after the supposed injury. He is belligerent, uncoöperative, and objects to questioning. He feigns tenderness on the slightest pressure and either refuses to attempt certain motions (such as kicking an imaginary football) or grossly exaggerates his actions while attempting them. He exhibits many tender spots, but when they are marked with a skin pencil he cannot relocate them on subsequent examinations. When he thinks he is not being watched, he may be observed to tie his shoe laces, or pull on his trousers normally (Forrester).

*Sciatica: Additional Comments.* Several reports concerned the subject of "sciatica" in a general way.<sup>118, 256, 533, 838, 875, 876, 914, 1021, 1041</sup> Classifications of the causes of sciatic neuralgia and neuritis were attempted.<sup>875, 1015</sup>

Sciatic fibrositis. According to Kersley most cases of "sciatica" are due to fibrositis either directly involving the nerve trunk or causing reflex pain from "fibrositic congestion and small cob-web adhesions in gluteal and lumbar muscles and posterior sacro-iliac ligaments." Others<sup>807, 838</sup> agreed with this view. Symptoms of "sciatic fibrositis" were said by Robinson to include "the type of pain common to all these syndromes," tenderness in gluteus medius or maximus, without muscle atrophy or abnormal tendon reflexes. [The problem of sciatic fibrositis is a very confused one. By this term some writers have meant a fibrositis of the investing tissues of the sciatic nerve. But current writers are using the term to designate not a perineural fibrositis but a fibrositis of muscles and tendons supplied by the sciatic nerve. In either case the condition is ill-defined because of inadequate pathologic data.—Ed.] Sciatic fibrositis was treated by the usual remedies for fibrositis: physical therapy, counterirritants, rest, later massage to sacro-iliac and gluteal regions, removal of infected foci and if necessary, manipulation or epidural injections (Kersley).

Previously considered (under "Effect of jaundice on atrophic arthritis") were the five cases of "sciatic neuritis" which preceded the onset of hepatitis and in which pain was relieved with the onset of jaundice (Lichtman).

For "sciatic pain of unknown origin" Haggart used a combination of two, sometimes three procedures: (1) perineural injection of the sciatic nerve, (2) traction to the affected extremity, (3) manipulation of the lower back under anesthesia. The majority of 75 patients so treated were benefited. Slot also used epidural injections of procaine hydrochloride and manipulation under anesthesia in cases of "rheumatic sciatica." Epidural injections were approved by Winkler but considered valueless by Duncan in cases of "sciatic pain." Other remedies recommended were short-wave diathermy, roentgen therapy, sinusoidal currents (Weiss) and the usual remedies; rest in bed on a hard mattress, Buck's extension, etc.<sup>256, 1041</sup> Injections into the nerve were condemned. Intramuscular injections of vitamin B (betaxin) were given by Stevenson to 18 patients with "sciatica": an equal number were "cured," "very much improved" and unimproved. Bennett and Cash treated 20 cases of intractable "sciatic neuritis" by fever therapy alone or with epidural injections: marked to complete relief was noted in 80 per cent.

### SPONDYLITIS

Most writers<sup>137, 278, 377</sup> accepted the traditional classification of the common forms of spondylitis; atrophic or ankylosing spondylitis (spondylitis rhizomelique) and hypertrophic spondylitis (spondylitis osteo-arthritis) and stressed the usual chief differential points as noted by Gordon: In hypertrophic spondylitis there is no ankylosis however extensive and numerous the osteophytes are; in atrophic (rheumatoid) spondylitis there is no vertebral lipping; in the former osteophytes represent true bone; in the latter what appears to be new bone is simply a deposit of lime salts in ligaments.

[Until recently physicians, including roentgenologists, paid little attention to parts of the spine other than vertebral bodies, but recently orthopedists and neurosurgeons have made much progress by studying the finer relationships among the intervertebral disks, foramina, spinal cord and nerve roots. As a result several "new" spinal syndromes have been described: herniated nucleus pulposus, degenerative fragmentation of disks with apophyseal subluxation, the facet syndrome, hypertrophied ligamenta flava, etc. Despite the broadened outlook of their colleagues it seems to us that most clinicians and rheumatologists have continued to consider spondylitis only in relation to the presence of exostosis or atrophy of vertebral bodies or of ligamentous calcification, and largely have ignored lesions of the only true joints of the spine—the apophyseal joints. Exclusive of such specific diseases as tuberculosis, brucellosis or Charcot's disease of the spine there are doubtless several "nonspecific" diseases of apophyseal joints and vertebral bodies that cannot be disposed of by the simple classification of atrophic and hypertrophic spondylitis. The recent introduction of the term "spondylarthrititis" to indicate disease of apophyseal joints in contrast to "spondylitis," a disease of vertebral bodies, may at first be confusing, but is distinctly a step in the right direction. Hence we have seen fit to present the following studies of Oppenheimer in some detail to serve as an introduction to some newer ideas on spinal pathology. Oppenheimer's classification probably will need much modification; the descriptions of some of his types were based on an experience with only a few (4 to 14) cases. Nevertheless his papers are stimulating and deserve attention. The

roentgenographic illustrations therein will clarify his conceptions better than we can here.—Ed.]

Oppenheimer presented a new classification based on a clinical and roentgenologic study of 147 cases. He considered it most important to distinguish between affections of the vertebral bodies (spondylitis), of the apophyseal or posterior intervertebral joints (spondylarthritis) and of the spinal ligaments (spondylosis ligamentosa). The vertebral bodies do not form true joints; the only true joints of the spine, that is those possessing a synovial membrane, are the small apophyseal joints. These may become affected by the various forms of arthritis primarily, independently, and exclusively of vertebral bodies, or, as parts of the vertebrae, may participate in localized or systemic diseases of the spine. Likewise the spinal ligaments may become affected alone (without disease of disks or apophyseal joints) as they do in Oppenheimer's type of spondylosis ossificans ligamentosa (not the same as Knagg's spondylitis ossificans ligamentosa), or the ligaments may calcify as a secondary manifestation of a variety of spinal lesions; e.g., spondylarthritis ankylopoietica, hypertrophic spondylitis, Pott's disease, and traumatic lesions. Hence Oppenheimer made the following definitions: (1) spondylitis, an inflammatory disease of the spine, especially the vertebral bodies, either rarefying, as in tuberculosis, or hypertrophic as in low-grade infections (he noted one form supposedly related to an amebic infestation) and in mechanical irritation resulting, for example, from thinning of disks; (2) spondylarthritis is an inflammation of the true spinal joints; i.e., the apophyseal intervertebral articulations; (3) spondylosis ossificans ligamentosa is an ossification of spinal ligaments which may appear with, but sometimes without, changes in vertebral bodies, intervertebral disks and apophyseal joints. "Calcification of spinal ligaments is a very common and totally uncharacteristic response to a great variety of vertebral lesions,—inflammatory, degenerative, destructive or traumatic."

[Oppenheimer seems to make no distinction between calcification and ossification.—Ed.]

1. *Spondylarthritis*. Four types of spondylarthritis were recognized: 1. Acute (atrophic) spondylarthritis (not the same as ordinary atrophic spondylitis) is a disease which is strictly localized (in five of Oppenheimer's cases to cervical, in two cases to lumbosacral spine) and represents an acute infection of certain apophyseal joints with inflammation of their synovia but the *cartilage remains intact* (the joint space does not disappear in roentgenograms). It represents a localized, usually monarticular, apophyseal arthritis with transient swelling of capsule which in Oppenheimer's cases was the aftermath of acute respiratory infection or chronic tonsillitis. [Does this represent an acute phase of the chronic type of spondylarthritis or of atrophic spondylitis?—Ed.] Since the vertebral bodies and disks are unaffected and the apophyseal cartilages remain intact, restoration of joint function is possible and occurred in several cases. "Acute atrophic spondylarthritis can be cured."

2. Chronic atrophic spondylarthritis is a type which also is not to be confused with ordinary chronic atrophic spondylitis but is a chronic *localized* disease of apophyseal joints, not of vertebral bodies or spinal ligaments; it is presumably infectious, characterized by capsular swelling, rarefaction of apophyseal bone, later irreparable destruction of apophyseal cartilage. "The distinction between acute and chronic

atrophic spondylarthritis is here not based upon the duration of the clinical symptoms, but is determined by the absence, in the former, of destruction of cartilage. Roentgenologically, therefore, the differentiation is made according to the width (normal or diminished) of the involved joint space. . . . Chronic atrophic spondylarthritis can be arrested by successful treatment of the coexistent infection."

"Atrophic spondylarthritis [the acute and chronic forms numbered 1 and 2] is independent of other systemic spinal diseases; there is especially no correlation either with spondylosis ossificans ligamentosa or with the various types of spondylitis."

3. Ankylopoietic spondylarthritis is a synonym for ordinary atrophic spondylitis, spondylitis rhizomelique, Strümpell-Marie's disease, Bechterew's disease, spondylitis ossificans ligamentosa of Knaggs. "This is a typical atrophic arthritis of the apophyseal joints (as proved histologically) with a marked tendency toward systemic involvement of all the apophyseal articulations and demineralization of the vertebral column. It is presumably an infection producing proliferative inflammation of synovial membranes, destruction of apophyseal cartilages, pronounced osteoporosis, fibrosis, later bony ankylosis of facets [this last being the criterion of the diseased] and secondary ossification of the ligamenta flava and longitudinal ligaments." Bony ankylosis produces the "bamboo spine" appearance: the vertebral bodies become rarefied, the disks (intervertebral spaces) remain normal or sometimes widen as they compress the softened vertebral bodies. As a rule the sacro-iliac joints are simultaneously involved, and the costo-transversal, hip and shoulder joints participate less commonly. The intervertebral foramina may be reduced in width to less than one-half of their original diameter by concentric calcifications. At earlier stages the swollen capsule also may compress the nerve roots. Whether or not such constriction will lead to actual compression of the nerves depends on the relation between the width of the foramina and the caliber of the nerves.

Oppenheimer stated, "It would appear justifiable perhaps to consider the three types of atrophic spondylarthritis—acute, chronic, and ankylopoietic, as phases of a single continuum without assigning to any single one or to all of them a specific cause. The pathological findings described may be the expression of reactions of these areas to stimuli of a number of kinds, but the reaction may stop at any point; or it may continue to the stage described as ankylopoietic spondylarthritis."

[We wonder whether the author's follow-up is sufficiently long to justify these statements.—Ed.]

4. Hypertrophic spondylarthritis also is an affection of apophyseal joints, not of vertebral bodies. Oppenheimer noted a "primary infectious form" in 14 cases, in 13 of which *Endamoeba histolytica* were found in the stools. The lesions were in the thoracic portion of the spine in seven, lumbar in three, cervical in four cases. Articular processes were greatly increased in density, facets were ragged, apophyseal joint spaces were irregularly narrowed, and there were thorn-shaped exostoses at the posterior borders of the contiguous facets: from two to many articulations were affected. Intervertebral spaces (disks) and vertebral bodies were normal. In three cases parts of the anterior longitudinal ligaments were calcified. Relief was obtained from anti-amebic treatment.

[Further evidence is necessary before accepting the view that amebae are responsible for this disease.—Ed.]

Another type of hypertrophic spondylarthritis was noted (a primary mechanical form) caused by mechanical irritation from traumatic or degenerative thinning of intervertebral disks and subsequent displacement of apophyseal cartilages. In apophyseal joints ulceration and degeneration of cartilage, eburnation of articular surfaces of the apophyseal joints, villous hypertrophy of the synovial membrane, hypertrophic exostoses, ossification of intra-articular ligament, then occur. Pathologic bony formations on contiguous facets may fuse, but this type of bony ankylosis is differentiated from that in ankylopoietic spondylarthritis by the absence of general rarefaction and the presence of residual exostosis.

All the forms of spondylarthritis so far described were regarded as being primary types to be distinguished from the secondary forms—diseases of *apophyseal joints* secondary to such conditions as tuberculosis, brucellosis, and osteomyelitis of *vertebral bodies*. As a matter of fact these diseases spread to apophyseal joints much more rarely than one might suppose. "It would seem that the distant position of the articular processes as well as the greater resistance of their compact bone prevents the [apophyseal] articulations from being easily affected." In osteoperiostitis, hypertrophic osteitis and Paget's disease articular processes may participate in the vertebral affection, but the apophyseal joint spaces often remain normal in width, and the outlines of the facets remain smooth. In general apophyseal cartilages remain intact unless statical alterations resulting from the disease of vertebral bodies secondarily induce degeneration of apophyseal cartilage and then hypertrophic spondylarthritis.

II. *Types of spondylitis*. Two chief types of *spondylitis* were recognized by Oppenheimer: (a) tuberculous spondylitis, a disease of vertebral bodies which affects apophyseal joints rarely (tuberculous spondylarthritis); (b) hypertrophic spondylitis, a disease characterized by exostoses at the margins of vertebral bodies, which may result, according to Oppenheimer, either from a low grade infection, or much more commonly from thinning of intervertebral disks. [We doubt that infection plays a rôle in hypertrophic spondylitis.—Ed.] In hypertrophic spondylitis, eburnation and exostoses of vertebral bodies, calcification of longitudinal ligaments and subluxation of articular processes occur. Some cases of hypertrophic spondylitis are associated with hypertrophic spondylarthritis. But only in 14 per cent of Oppenheimer's 72 cases of hypertrophic spondylitis was there also secondary hypertrophic spondylarthritis (eburnation of facets, exostoses at the articular processes of apophyseal joints).

*Relationship between Hypertrophic Spondylitis and Hypertrophic Spondylarthritis*. As indicated in the foregoing discussion the apophyseal joints may be affected in one way or another without similar reactions occurring in vertebral "joints" and vice versa. Hence hypertrophic spondylarthritis may occur without hypertrophic spondylitis, and hypertrophic spondylitis may (and generally does) occur without hypertrophic spondylarthritis. "This is not surprising, for the apophyseal joints differ in both structure and function from the intervertebral synchondroses formed by the disks and the adjacent vertebral surfaces. The vulnerability of the articular cartilage is variable in different persons; therefore mechanical stress does not of necessity lead in every instance to lesions of cartilage inducing arthritis. Hypertrophic spondylitis is very often the result of lesions of the disks. On the other hand thinning of the disks does not invariably lead to increased bone formation at the vertebral bodies. Similarly the abnormal stress upon the facets in this condition does not of necessity induce lesions of cartilages. It would seem that both the vulnerability of the cartilage and the readiness of the bone to respond by formation of exostoses are important factors in the pathogenesis of these conditions. This is shown by those instances in which no bone reactions develop at both the vertebral bodies and the articular processes in spite of marked thinning of the disks, contact between the bodies and pronounced thinning of the articular cartilages." In these cases none of the characteristics of hypertrophic arthritis become evident roentgenographically; only the intervertebral and the joint spaces seem to be affected; bones are not involved. But in thinning of disks, enormous exostoses may occur on the corresponding vertebral bodies without narrowing of the apophyseal joint space or change in facets. This indicates that vertebral bodies responded to the abnormal mechanical stress produced by the thinning of the disks, but cartilages resisted. "Regardless of the presence or the absence of these secondary changes, thinning of disks is the cause of their eventual development, for it leads to contact between vertebral bodies, to abnormal tension upon ligaments, to displacement of articular processes, and to narrowing of the intervertebral foramina." The type of spondylarthritis that develops under these circumstances was called the "discogenetic" form of hypertrophic spondylarthritis.

*III. Spondylosis Ossificans Ligamentosa.* This condition was distinguished from the secondary ligamentous ossification that is associated with several spinal diseases (notably ankylopoietic spondylarthritis) and was described by Oppenheimer as a systemic ossification of ligaments without changes of disks or apophyseal joints, usually discovered accidentally during examinations of chest in persons over 50 years of age without clinical symptoms. Apophyseal joints remain normal. Posture is not altered. Involvement was greatest in the less mobile thoracic portion of the spine, least in the more mobile cervical and lumbar regions; hence spinal mobility usually seemed intact.

#### ATROPHIC SPONDYLITIS (SPONDYLITIS ANKYLOPOIETICA)

*Clinical Data.* Most writers classified this as atrophic (rheumatoid) arthritis of the spine. Others<sup>377, 982</sup> concluded that it is closely related to, but not identical with, atrophic arthritis, among other reasons because the sex incidence is reversed and because of serologic differences between the two conditions. The usual clinical data were reviewed.<sup>137, 377</sup> Scott repeated his argument that the pain and stiffness of the lower part of the spine and sacro-iliac joints are quite late, not early signs of the disease. According to him the initial pre-spondylitic symptoms begin generally about the age of 12 to 14 years as wandering pains in limbs, joints, chest and abdomen at which time roentgenograms of sacro-iliac joints do not reveal any abnormality; perhaps two years later the pre-spondylitic symptoms "begin in earnest" with more definite pains in knees, chest, shoulders; at this time roentgenographic changes in sacro-iliac joints are already present despite which there is as yet no stiffness, backache or sacro-iliac pain. By the time sacro-iliac and low back pain begins the disease is thought by Scott to be several years old. "Pathologic changes can be detected in sacro-iliac joints about six or seven years before there are any clinical signs whatever of arthritis in the spine." Scott stated that "sacro-iliac changes" were pathognomonic of this type of spondylitis "for they have been present in all of the 300 patients under observation." If roentgenograms of sacro-iliac joints were to be made of young patients with recurrent attacks of rheumatic pains in various parts, "spondylitis adolescens" could be "recognized several years before the backache period commences." This view was not acceptable to others. Thus Gordon wrote "Scott's contention that every case shows evidence of sacral ankylosis cannot be supported by observers whose clinical experience is at all extensive."

*Laboratory Data.* Arneth counts were similar to those in cases of atrophic arthritis.<sup>357</sup> Spondylitics with elevated sedimentation rates also showed the formol-gel reaction most frequently.<sup>360</sup>

*Etiology.* Nothing definitely new on etiology was presented. The French concept that gonorrhea can cause chronic atrophic spondylitis was disputed.<sup>137</sup> In previous papers Scott suggested that an infection of the sacro-iliac joint was the chief focus, eradication of which by excision or roentgen therapy might stop the spread of the disease. In his current paper he seems to have altered his position somewhat for he stated, "The only explanation of the results [of roentgen therapy] is that these small doses,



given as 'x-ray baths,' stimulate the ductless gland system." In Van Dam's opinion "it is unnecessary to postulate any focus in these joints. The clinical evidence also gives little support."

*Treatment.* The usual measures were again advocated: removal of infected foci, rest for body and especially for the spine, rest in plaster shells several hours daily, spinal brace, breathing exercises 10 minutes daily to maintain mobility of the costovertebral joints, exercises for hips and shoulders, various forms of physical therapy, and general measures such as cod liver oil.<sup>187, 877</sup> The use of stock polyvalent streptococcal vaccine seemed "justifiable"<sup>187</sup> but its results were unimpressive. Results of treatment with gold salts also were "disappointing" but "more promising than vaccine" according to Buckley who also prescribed calcium gluconate "to make good the calcium wastage." [We strongly doubt the efficacy of such a remedy.—Ed.] The use of forcible manipulation was condemned.<sup>187, 877</sup> Unilateral lumbar sympathectomy was done in one of Buckley's cases of ankylosing spondylitis with painful spasms of legs. "The results were satisfactory and the patient was able to walk better afterwards as well as being relieved of the pain and spasm. The operation will be repeated on the other side, if the improvement is maintained."

[We do not see how lumbar sympathectomy could in any way influence the spinal pathology of this disease.—Ed.]

Roentgen therapy was recommended. According to Van Dam three types of roentgen therapy are used: (1) penetrating rays as used by the majority, (2) the softer rays which are absorbed and are not penetrating, these two types being applied to joints, and (3) irradiation of sympathetic ganglia of the neck in addition to irradiation of the lumbar spine. Gordon and Scott considered deep roentgen therapy "absolutely contraindicated." But Scott was again enthusiastic about his results with "wide field" irradiation. "If the dosage is correct, interesting results are noticed; the patients put on weight, do better work, do not get tired, become symptom-free, etc." He mentioned "striking" results, among them the return of painless "unrestricted movements" four months after treatment in a "hopeless" case of "complete poker back."

[It is difficult for us to share Scott's enthusiasm for such treatment. Although he has written of it for three or four years, he still has published no statistical or clinical details of his results.—Ed.]

### HYPERTROPHIC SPONDYLITIS (SPONDYLITIS OSTEO-ARTHRITICA)

*Clinical Data.* This disease was commonly accepted as the spinal equivalent of hypertrophic (osteo-) arthritis in peripheral joints.<sup>187, 982</sup> The well-known clinical symptoms were reviewed.<sup>877, 838</sup> According to Gordon the chief cause of pain and stiffness in these cases is not the osteo-arthritis but its associated fibrositis. Compression of nerve roots results occasionally from osteophytic lipping (which is generally on the anterior surface of the

vertebral bodies well away from the foramina) but more often from dense fibrous cartilage which often spreads extensively round the osteophytes.

[According to Oppenheimer's concept compression of nerve roots is more closely related to the amount of hypertrophic spondylarthritis present than to the amount of hypertrophic spondylitis present.—Ed.]

Cavenagh reported the unusual case of a man, aged 56 years, who had marked hypertrophic arthritis of several cervical vertebrae and extensive bilateral ossification of stylohyoid ligaments.

*Treatment.* Heat and massage were, of course, generally recommended. Relief of pain following fever therapy was noted by three patients of Bennett and Cash. Terhune approved Hanflig's (1936) method<sup>4</sup> of repeated stretching of the neck in cases of cervical arthritis. "Some measure of relief" was noted by all of 10 patients so treated. Roentgen therapy was approved by Van Dam, but considered by Scott "uncertain in its results." Roentgen-rays of medium wave length were used in early cases with "good results" (Scott). Buckley noted some relief of muscle spasm with deep roentgen therapy.

#### GOUT AND GOUTY ARTHRITIS

Interest in gout has sharply increased; a few years ago only three to six papers on it appeared annually in English and American literature; about 30 papers were available for this review.

*Incidence.* From current literature gout seems to be leaving its old homestead in England, and has at last caught up with the children of the Pilgrims in America. English investigators wrote: "Acute classical gout is steadily diminishing"<sup>955</sup>; "tophaceous gout is almost a condition of the past."<sup>18, 19</sup> But in the United States the relative ease with which Cohen, and Vorhaus and Kramer respectively collected 41 and 25 cases of classical gout within a short time convinced them that the disease is common in this country. "The apparent rarity of gout is in reality due to a diagnostic unawareness of it."<sup>992</sup> Van Breemen considered it rare in Holland; there were only seven cases of "old-fashioned gout" among the 20,000 to 25,000 rheumatic cases encountered by him in five years. It is common in Sweden: gout was present in about 10 per cent of the cases of acute polyarthritis and 4.5 per cent of cases of chronic arthritis seen by Kahlmeter in four large general hospitals in Stockholm. The incidence of gout among rheumatic patients at Aix-les-Bains has not changed in the past 60 years; it is still about 1 per cent (seven patients with gout among 800 rheumatic patients). Its incidence in Paris among privately treated rheumatic patients was about 2 per cent, among rheumatic patients treated in hospital 1.2 per cent (Coste, Forestier and Certonciny). Moreno considered gout rare in the Argentine even though the natives are heavy meat eaters. But its incidence among his rheumatic patients was also about 2 per cent. Hill warned that statistics on incidence are difficult to evaluate and dangerous to accept; in the Devonshire Royal Hospital (Buxton) the incidence during 50 years varied notably from

time to time depending on the personal reactions of the changing staff to a diagnosis of gout.

*Factors Governing Incidence.* Chief factors governing incidence of gout are heredity, sex, age, occupation, personal habits, geography, race, and climate.

1. Heredity. The factor of heredity continues to be most "obvious" among English cases (in 45 per cent of Hill's 93 cases, in 22 per cent of the 54 cases of Gibson and Kersley), much less obvious elsewhere (rare in Sweden<sup>511</sup> and in the Argentine<sup>679</sup>; present in only seven of 120 cases in Vienna<sup>334</sup>; in only four of 41 cases in Philadelphia).<sup>195</sup>

2. Sex. This is again a dominant factor in all series. Gout is rare among females; about 90 per cent or more of the patients are males. In the new series females were affected in the following percentages, 5,<sup>489</sup> 8,<sup>938</sup> 9.8,<sup>195</sup> 10,<sup>334</sup> 11,<sup>359</sup> 20,<sup>861</sup> 22.5,<sup>449</sup> 36.<sup>992</sup> [The statistics in the last three series are distinctly out of line with the common experience and make one suspect the validity of the diagnostic criteria. Among Hill's 93 patients, 21 of whom were females, were 15 with abarticular gout (mostly fibrositis). The clinical description of Vorhaus and Kramer was orthodox enough but no details concerning their nine female patients (out of 25 patients) were given whereby the reader could evaluate the diagnosis. Vorhaus and Kramer gave an exhibit, presumably based on these same cases, at the meeting of the American Medical Association in 1937; at that time some of us could not accept the diagnosis of gout in a few of his cases among women. The condition seemed to be hypertrophic arthritis with Heberden's nodes. Whether these cases were excluded later from his report or whether their inclusion explains the high incidence of females among his patients cannot be stated by us. However, one of the women seen by them had her first attack at the age of 12 years and had many tophi by the age of 27 years.—Ed.] Thomson presented a view commonly held in England, but not in the United States, that gout affects women more often in a nontophaceous, atypical, rather chronic form resembling atrophic arthritis, than in the classical form. In all of Freund's cases of gout among women classical gout with hyperuricemia, recurrent acute attacks of arthritis and complete remission was present. Five women with tophaceous gout were seen,<sup>334, 449, 938, 992</sup> and also a woman with pretophaceous gout whose first attack was at the age of 64 years and whose father had gout (Halsted).

3. Age. Articular symptoms first appeared in most cases between the ages of 35 and 45 years, occasionally in the early twenties.<sup>350, 449, 489, 603</sup> The first attack affected six patients in their teens,<sup>938, 992</sup> one patient at 64<sup>408</sup> and one at 72 years of age.<sup>359</sup>

4. Occupation. Those frequently affected were "publicans" with opportunities for alcoholic imbibition,<sup>449</sup> and coachmen in England,<sup>930</sup> commercial travelers and railway workers in France.<sup>220</sup> Gout was rare among miners and other workers in heavy manual occupations who are subject to profuse sweating.<sup>449</sup>

5. Personal habits. Those addicted to excesses in food and drink were said to be affected by more numerous and severe attacks, but the disease often affected temperate persons.<sup>408</sup>

6. Geography and race. This factor has been mentioned previously. Gout is rare in colored people. Two American negroes were affected.<sup>142, 195</sup>

7. Weather and climate. According to Coste and Forestier intense cold is bad for gouty patients; it may precipitate acute attacks. In general gouty patients can rarely forecast storms from articular symptoms<sup>938</sup> and no real meteorologic influences were noted in 100 cases of severe gout.<sup>219</sup> However, other studies by Talbott and Coombs suggested that barometric changes affect significantly the metabolism of gouty patients.

*Clinical Data.* 1. Prodromes. Many patients (50 per cent according to Moreno) experience no prodromal symptoms before an acute attack; some

have dyspepsia and mental depression<sup>956</sup>; others note euphoria<sup>359</sup> or a ravenous appetite as a symptom of the disease.<sup>195</sup>

2. Provocatives. The provocative effects of season, diet, operations, infections, certain chemicals or medicines, and emotional upsets were discussed. Acute attacks occurred most often in spring, much less often in autumn or at other times.<sup>449</sup> In some cases attacks were precipitated by a particular drink or a food not necessarily rich in purine.<sup>359</sup> The female patient of Halsted ate sparingly of meat and rarely took alcohol. Attacks were precipitated by appendectomy in one case, by iridectomy in another.<sup>195</sup> Post-operative attacks were blamed on enforced rest by Van Breemen, on decay of cells incident to operation by Freund. Operations will not always provoke an acute attack, but only in certain cases and at certain times. Thus the patient of Ludwig, Bennett, and Bauer escaped an attack after tonsillectomy within one month of an attack. [Many attacks appear without discoverable provocation. In the experience of one of us, P. S. H., some patients seem to be temporarily more resistant to an attack during the first few weeks after an attack; during this time they are more likely to endure an operation without postoperative flare-up of their gout.—Ed.] Patients with quiescent rheumatic fever may experience a flare-up after any surgical operation but the postoperative exacerbations of rheumatic fever generally occur seven to 14 days after operation<sup>603</sup>; those of gout, usually within five days after operation (Hench, 1935). Acute or subacute coincident infections may provoke acute gout: in one case acute gouty arthritis always developed after an acute "nasal and bronchial catarrh."<sup>359</sup> Shock at the death of a relative, or financial losses suffered by bankers and speculators were cited as precipitants of an attack.<sup>359, 408, 980</sup>

3. Chemical and medicinal provocatives. "Lead gout" (classical acute gouty arthritis precipitated by lead poisoning from drinking water) is still seen in Holland.<sup>980</sup> Injections of gold are said to precipitate attacks in some cases but not in others.<sup>679</sup> The provocative effect of salyrgan was noted previously.<sup>4</sup> Price noted five patients with congestive heart failure, each of whom received on alternate days 1 c.c. of salyrgan intramuscularly and 60 grains of ammonium chloride orally. Within seven to nine days after the first dose copious diuresis of urates and sodium chloride occurred, which was followed at once by acute gouty arthritis. Apparently the salyrgan reproduced disturbances of electrolyte balance similar to those seen in spontaneous attacks by Talbott, Jacobson and Oberg.<sup>3</sup> Three patients given salyrgan by Jacobson had markedly increased quantities of uric acid in urine and decreased quantities in blood, but no attacks were precipitated. To the list of medicinal provocatives previously reported two new ones can be added, decholin (synthetic bile acid, dehydrocholic acid) and thiamin chloride (vitamin B<sub>1</sub>). To an elderly gouty patient three weeks after an acute attack Bowers gave decholin (3¾ grains t.i.d) as a choleric. Within 36 hours after the first dose the joints of both great toes were acutely af-

fected; the drug was stopped and within 48 hours the acute gout disappeared completely.

[This case suggests that decholin may be a provocative, but more information is necessary.—Ed.]

Of special interest are the studies of Vorhaus and Kramer on the effect of vitamin B<sub>1</sub> (thiamin chloride) on gout. The daily oral and parenteral administration of from 1 to 10 mg. (330 to 3,300 international units) promptly provoked acute gouty arthritis in 92 per cent (23) of 25 patients so treated. Attacks usually appeared within two to four, occasionally 10 to 14, days after beginning such therapy and lasted 5 to 10, occasionally 14 days. Reactions were mild in 12, moderate in 8, severe, with fever and disability, in three cases. Despite initial reaction, medication was continued, was thereafter borne well, and seemed of therapeutic value.

[One of us, W. B., has been unable to corroborate these findings.—Ed.]

Acute attacks appeared at night in 84 per cent of Hill's cases. He could not prove the idea that nocturnal attacks occur because a slowed nocturnal circulation presumably favors the precipitation of urates or because at night an increased vagotonia and slight alkalosis supposedly occur. Some physicians are not aware that attacks may or may not be febrile; in current cases temperatures of 102°, 408 104° or even 105° F. were noted.<sup>359</sup>

Some physicians hesitate to diagnose gout unless a large toe is affected. Podagra (involvement of a large toe) may or may not occur in initial or subsequent attacks. It occurred in the first attack in 15 of Sherwood's 20 cases, in only seven of the 28 cases of Vorhaus and Kramer. A foot was affected in the first attack in 18 of the 24 cases of Talbott and Coombs. Shoulders and hip joints are rarely affected even in late attacks. Shoulders were affected with other joints in one case,<sup>408</sup> hips in three cases,<sup>992</sup> ankles, knees and hips in one case.<sup>603</sup> In Cohen's cases initial attacks were monarticular in 14, polyarticular in 27. In the opinion of the majority, chronic gouty arthritis invariably is preceded by repeated acute attacks with complete remissions.<sup>408, 603, 679, 861</sup> Others<sup>195, 359, 955</sup> stated that gouty arthritis may at times appear insidiously and progress chronically without complete remissions, especially among women.<sup>449</sup> Gibson and Kersley, and Thomson concluded that in some cases classical gout appears at first but develops into a clinical condition indistinguishable from rheumatoid or villous arthritis; hence they suggested the existence of the hybrid, "rheumatic gout," or the coexistence of both gout and rheumatoid arthritis in the same case.

[Such terminology seems to us to increase the existing confusion.—Ed.]

[If such a coexistence occurs, it is extremely rare in our experience.<sup>2</sup> Freund saw one such case. The supposed association of gouty arthritis and nongouty atrophic arthritis in a given case cannot be proved without adequate pathologic studies. In the case of Ludwig, Bennett and Bauer such a combination might have been supposed to exist because spindle shaped joints, ankylosis of several joints and positive streptococcal agglutination tests were present in addition to tophi, but pathologic studies revealed only chronic gouty arthritis in various stages, producing in some joints the general appearance of atrophic arthritis. We agree with Moreno that, because of forgetfulness of minor attacks not considered gouty, some patients erroneously intimate that their gouty arthritis began in chronic fashion.—Ed.]

4. Tophi. Woolner's marks, sebaceous cysts and Heberden's nodes are too often called "tophi." No nodule should be considered a tophus until urate crystals have been discovered therein.<sup>129</sup> Subcutaneous tophi were found in 24,<sup>359</sup> 32,<sup>992</sup> 43,<sup>449, 489</sup> and in 58 per cent<sup>938</sup> of current cases. They are supposedly rare in Sweden.<sup>511</sup> Christopher and Monroe noted a patient

who had had many acute attacks and presented large ulcerating tophi at the heels which five times had been considered to be due to pyogenic ulcers.

*Unusual Clinical Features.* A patient of Ludwig, Bennett and Bauer had severe tophaceous gout with flexion deformities of knees and fingers, and ankylosis of multiple joints. The condition superficially resembled chronic atrophic arthritis. The patient already had chronic gouty arthritis, having had seven or more acute attacks within five years. Markel reported a case of gout with erythromelalgia; the latter, unrelieved by a regimen for gout, was relieved by injections of typhoid vaccine. Burman performed arthroscopy on the knee of a gouty negro and noted a peculiar fluorescence of the synovial fluid and membrane caused by the presence of bile pigments from mild unsuspected jaundice. Diabetes affected four of Freund's 120 patients.

*Irregular Gout.* Certain writers accepted the following cases as manifestations of gout: some cases of chronic arthritis without tophi but with transient hyperuricemia,<sup>359</sup> erythema and palmar or plantar hyperkeratosis,<sup>50, 449</sup> certain cases of eczema and urticaria,<sup>50</sup> "gouty" neuralgia, myalgia and sciatica,<sup>1013</sup> trigeminal neuralgia (two cases of the last with hyperuricemia, relieved by colchicine and atophan "when all else had failed"),<sup>449</sup> other conditions supposedly caused by "gouty diathesis" and ranging from so-called rheumatism to eczema.<sup>19</sup> Others noted "indigestion," eczema and pruritus in few or none of their cases of gout.<sup>449, 992</sup> According to Buckley<sup>136</sup> and Thomson, gouty patients suffer so often from fibrositis that the latter may be considered a true symptom of gout. Hill noted 14 cases of "gouty fibrositis" and 21 cases of "gouty arthritis and fibrositis" in which the same biochemical findings and responses to "specific" remedies occurred as in cases of gouty arthritis. A rapid effect from colchicine was noted by seven of eight patients to whom it was given. Gout, however, is rarely the cause of fibrositis: there were only 15 cases of gouty fibrositis "among 8000 to 12,000 cases of fibrositis" seen by Hill. Accepted as gout by Gilbert and Kersley was a case of recurrent lumbago in which the value for blood uric acid was 4.7 to 5.6 mg. per cent. "Neuromuscular tenderness" affected 18 of Vorhaus and Kramer's 25 patients with gout. Many instances of irregular gout ("gouty iritis, gouty phlebitis") have been proved to be due, not to gout, but to septic foci, according to Brown<sup>129</sup> who was "skeptical as to suppressed, and agnostic as to irregular gout."

[We share Brown's skepticism. The data currently presented in favor of the existence of irregular gout continue to be unconvincing. No pathologic studies on tissues related to the symptoms in cases of irregular gout were reported, and only occasionally was precise information given on the effect of colchicine or other remedies for gout.—Ed.]

*Complications.* Renal insufficiency, generally mild, affected seven of Jacobson's 21 patients. The patient of Ludwig, Bennett and Bauer passed urinary gravel composed of urates in the fifth year of his gouty arthritis. In 25 per cent of Freund's cases kidney stones (generally urate, sometimes oxalate or phosphate) developed; urate stones developed in four of the 24 cases of Talbott and Coombs; renal colic from urate stones occasionally preceded the first attack of gouty arthritis.<sup>334, 938</sup> Of itself the passage of urate gravel or stones does not justify a presumptive diagnosis of gout. [But it should certainly initiate a thorough examination of the patient for gout.—Ed.]

Talbott and Coombs found no clinical or laboratory signs of gout in several such cases, and Mann described the symptoms and clinical findings in a number of nongouty patients affected by uric acid showers and renal stones. Of 136 renal stones analyzed by Mann 10 per cent were uratic. Among 50 cases of renal colic Sherwood found five of gout. The pathologic effect of nongouty urate deposits in kidneys was described.<sup>481</sup>

Vascular degeneration is another accepted complication of gout. Marked arteriosclerosis with marked, vascular calcification, visible in roentgenograms, affected the 28 year old patient of Ludwig, Bennett and Bauer.

*Laboratory Data.* Anemia is usually absent.<sup>861</sup> Gibson and Kersley found slightly reduced volume of erythrocytes, an increased percentage of neutrophils in differential blood counts, and in Arneth counts a shift to the left even greater in gout than in atrophic arthritis. According to Sherwood "the very nature of gout is incompatible with an alkaline urine. . . . Hence an alkaline urine renders a diagnosis of gout improbable." [We cannot agree with this statement. Alkaline urine is often found in cases of gout. But it might be correct to say that the formation of urate gravel and stones in the renal pelvis and calices (but not in renal parenchyma) is incompatible with alkaline urine.—Ed.] The pH of blood was normal in 125 cases, slightly low in four, increased in only one of Hill's cases. This refutes the theory that in gout the pH of the blood is abnormal. Blood calcium was generally normal.<sup>449</sup>

In many cases the sedimentation rates are markedly elevated (sometimes nearly as much as in rheumatic fever)<sup>511</sup> during acute attacks and rapidly return to normal as attacks subside.<sup>408, 449, 511, 603, 679, 861</sup> Gibson and Kersley found no clinical or statistical relationship between sedimentation rate and level of blood uric acid. In some cases of gout formol-gel reactions were weaker than the sedimentation rates warranted.<sup>859</sup>

*Relation of Blood Uric Acid to Gout.* Sooner or later practically all gouty patients have hyperuricemia. The concentration of uric acid in whole blood was 4 mg. or more per 100 c.c. (Folin method, 1924) in 59 per cent of the cases of Gibson and Kersley, 4.5 mg. or more (Folin direct method) in about 90 per cent of Hill's cases, and more than 6 mg. (method unstated) in 72 per cent of the cases of Vorhaus and Kramer. Hyperuricemia, however, does not develop in any constant pattern and there is no constant relationship between the duration of gout and the amount of hyperuricemia.<sup>136, 679</sup>

Many patients exhibit hyperuricemia early in the disease,<sup>489, 603, 938</sup> but others may experience several attacks of gouty arthritis, yet exhibit no hyperuricemia.<sup>334, 679, 861</sup> The concentration of uric acid in blood was less than 4.5 mg. in 13 of Sherwood's 20 cases, and "in over 40 per cent of cases of clinically typical gout a high reading [4 mg. per cent or more] was never obtained" by Gibson and Kersley. Patients may even present tophi without hyperuricemia (as in case 3 of Gibson and Kersley). [Such cases are rare.—Ed.] Therefore one must not insist on the presence of hyperuricemia before entertaining a diagnosis of gout.<sup>136, 195, 334, 359, 679, 861</sup>

[Likewise the presence of hyperuricemia is not sufficient for a diagnosis of gout: Gibson and Kersley noted hyperuricemia in 2 per cent of 251 cases of undoubted atrophic arthritis, in 5.4 per cent of 184 miscellaneous nongouty rheumatic cases. The serum uric acid in 3 per cent of Jacobson's 100 nongouty patients was 6 mg. per cent or more.—Ed.]

There is also no constant relationship between the level of blood uric acid and the acute attacks of gouty arthritis.

In some cases the level of blood uric acid apparently increased during acute attacks and decreased thereafter; in others it did not.<sup>136, 195, 449, 1013</sup> Gibson and Kersley noted no constant relationship between sedimentation rates and the level of blood uric acid during acute attacks. Rates were generally increased, but the level of blood uric acid did not rise consistently. Therefore they concluded that if the sedimentation rate indicates the severity of the local tissue reaction, the extent of hyperuricemia must be independent of that process. "The findings appear to indicate that the hyperuricemia is incidental and not an essential part of the disease."

[Nevertheless it is an important feature in the disease.—Ed.]

The concentration of uric acid in serum was compared by Jacobson to that in the whole blood of 21 gouty and 100 nongouty persons. It was concluded that estimations of uric acid in serum (from blood collected and allowed to clot under oil) are more accurate and much less variable than those done on whole blood. Exposure of blood to air appeared to increase the uric acid content not only of whole blood but also of serum. For example the content of uric acid in one sample of whole blood collected in the routine manner and exposed to air was 7.6 mg. per cent; that of a sample of the same person's blood collected at the same time and handled anaerobically was 6.8 mg. per cent. The uric acid in serum of blood clotted in air averaged about 0.5 mg. per cent higher than that in serum of blood clotted under oil. The concentration of serum uric acid (from blood collected under oil) was practically always higher than that of whole blood (collected under oil), but was about equal to that of plasma (handled anaerobically). The new technic was used in determining the levels of *serum* uric acid at different stages of gout in 21 cases during and between attacks. The concentration of uric acid in serum ranged from 5.2 to 14.8 mg. per cent. In about 98 per cent (174) of 177 tests the value exceeded 6 mg. per cent; in 167 tests (about 94 per cent of the total) it exceeded 7 mg. per cent. In four cases the serum uric acid fluctuated markedly both during asymptomatic intervals and during attacks of acute gouty arthritis. Many of the fluctuations were associated with drug (aspirin, colchicine, salyrgan) therapy. In one case, studied intensively for a year, the serum uric acid fell significantly within three days preceding the acute attacks and did *not* rise, but remained unchanged during the attacks. In four cases an apparent direct correlation was found between the highest concentration of serum uric acid and the severity of the disease.

In the cases of Talbott and Coombs the minimal values for *serum* uric acid were 5.7 to 10.4, the maximal values were 6.6 to 14.2 mg. per cent. Gibson and Kersley also compared the uric acid content of plasma and whole blood. In atrophic arthritis values in plasma averaged 0.77 mg. per cent higher, in gout 1.97 mg. per cent higher than those in whole blood.

[When studying these reports on concentrations of uric acid the reader must readjust his ideas on the upper limits of normal: whereas it is 4.5 mg. per cent in whole blood, it is 6 mg. per cent in serum or plasma. In Jacobson's cases of gout the *serum* uric acid was practically always over 6 mg. per cent, but Gibson and Kersley noted values in *plasma* (presumably the equivalent of values in serum) as low as 4.7 mg. per cent. Others of us, M. H. D. and P. S. H., not infrequently have noted values of serum uric acid below 6 mg. in cases of tophaceous, as well as in cases of classical pretophaceous gout. But the method of Jacobson should be called to the attention of laboratory technicians, particularly the colleagues of those concerned with arthritic cases.—Ed.]

The uric acid content of synovial fluid of nongouty controls equalled that of plasma and averaged 1.06 mg. per cent higher (range 0.2 to 2.0 mg. per cent) than that of whole blood (Gibson and Kersley).



In the case of Ludwig, Bennett and Bauer during attacks of gouty arthritis the urinary uric acid increased notably, but there were no consistent changes in the serum uric acid: The mean value for serum uric acid during attacks was  $12.4 \pm .2$  mg. per cent, between attacks  $12.1 \pm .3$ .

*Roentgenograms.* These are of little diagnostic value in early stages of gouty arthritis.<sup>511, 532</sup> They may be "negative," as they were in 50 per cent of Sherwood's cases, or they may show a variety of nonspecific changes as they did in 96 per cent of the cases of Vorhaus and Kramer. In the latter the average duration of the gout was seven years among patients with slight roentgenographic changes, nine years among those with moderate changes, and 11.6 years among those with marked changes. Weissenbach and Françon gave the name "thorn foot" to the [nonspecific hypertrophic] exostotic reactions in articular bone at the upper surface of the tarsus in seven cases. When roentgenograms become really helpful the diagnosis is generally obvious on other grounds.<sup>511</sup> In the severe case of Ludwig, Bennett and Bauer a variety of "specific" and nonspecific hypertrophic and destructive changes appeared, and three unusual features: ankylosis of several joints, involvement of a sacro-iliac joint and small areas of erosion at the articular surfaces of femur and tibia at a knee joint. Areas of erosion at large joints are "extremely rare"; for diagnosis one should obtain roentgenograms of hands and feet and not rely on those of large joints. Even so areas of erosion are not necessarily gouty, but may occur in cases of atrophic and hypertrophic arthritis, lupus pernio and cystic diseases of bone (Golding). Hence roentgenographic changes, although helpful, should never be considered final or conclusive evidence for gout.<sup>559, 980</sup>

*Pathology.* It is not easy to find in American literature descriptions of the pathologic reactions of gout. The articular changes in their case were described in detail by Ludwig, Bennett and Bauer. To preserve the specific gouty (uratic) lesions the tissues must be fixed, not in formalin or the usual formalin-containing fixatives (which rapidly dissolve the urates), but in absolute alcohol and stained with silver nitrate (de Galantha method<sup>3</sup>). Sodium urate crystals may be deposited in cartilage, synovial membrane, perichondrium, subchondral bone, bone marrow, periosteum, fibrous capsules, adjacent ligaments, tendons and bursae, especially the olecranon bursae. Wherever the deposits occur they invoke a foreign-body, giant-cell reaction with proliferation of fibrous tissue and small collections of lymphoid cells. The extent of articular change that occurs depends on the amount of urates deposited, their situation and the resultant reaction to them. These reactions may include regional destruction of cartilage and subchondral bone, overgrowth of cartilage and bone ("hypertrophic arthritis") at articular margins, synovial fibrosis and formation of pannus which may (rarely) cause ankylosis. The pannus is studded with urate deposits which distinguish such a pannus from that of atrophic arthritis.

Vascular sclerosis may occur in the region of urate deposits and elsewhere. Notable arteriosclerosis was present in the legs of one 28 year old

patient.<sup>603</sup> The finding of such changes supports the aphorism of Huchard that gout is to the arteries what rheumatic fever is to the heart. Hill regarded the various forms of arrhythmias and anginal pain seen in gout the result of myocardial ischemia from coronary sclerosis and not due to specific gouty lesions.

"Gouty teeth," yellow worn-down teeth with exposed dentures, have been considered signs of a gouty constitution. But Gibson and Kersley<sup>531</sup> saw nongouty persons with such teeth, and gouty patients without them; they found no histologic difference between the teeth of gouty and nongouty persons.

*Diagnosis of Gout.* The fact that in one series of 25 cases an average of 8.8 years elapsed between the first attack of gouty arthritis and the first diagnosis of gout constitutes an indictment of the prevailing attitude toward gout (Vorhaus and Kramer). Physicians currently do not think of gout or will not make the diagnosis unless a big toe is affected or hyperuricemia or even tophi are present. Absence of these features in a given case, however, must not prevent a diagnosis of gout if other significant data are present.<sup>334</sup> The commonest source of error is an incomplete case history.<sup>195</sup> The most important single diagnostic feature is an accurate history describing the characteristic features of the single attack and the continuing pattern of acute attacks with complete remissions.<sup>350, 603, 956</sup> The delayed excretion of uric acid by a patient on a diet rich in purines was considered of no diagnostic value; such delays also occur in cases of atrophic arthritis and are nonspecific (Freund). The provocative tests used by Gibson and Kersley gave inconclusive results. Ketogenic diets were given in seven cases of gout (and in three control cases): moderate ketosis resulted but no change in the concentration of urinary uric acid. Among 11 gouty patients given a ketogenic diet the blood uric acid increased moderately but only three had "more discomfort" and only one an acute attack. Thus a ketogenic diet could not be used as a hard and fast provocative test in borderline cases. For periods of a week each, stimulants of the sympathetic nerves (ephedrine and bellafolin, an atropin preparation) and of the vagus (ergotamine tartrate) were given in unstated amounts: of eight patients so treated six noticed no change; only two noted any real change—these were better from the sympathetic, worse from the vagal stimulants. Therapeutic tests, such as relief with cinchophen or with diet, are not sufficiently specific to be of unquestioned diagnostic value. The most convincing and specific test is "the quick answer to colchicum" (Moreno).

*Etiology.* No new ideas on etiology were reported. Most writers now believe that the hyperuricemia is not the cause of the disease but only a symptom<sup>129, 532, 956, 1013</sup> and that gout is a metabolic disturbance of some sort possibly related to hepatic dysfunction.<sup>135, 954, 980, 1013</sup> The human liver is notably concerned with the formation of uric acid. Hepatic enlargement,<sup>195</sup> epigastric heaviness and oppression possibly caused by hepatic con-

gestion,<sup>449</sup> and abnormal results of levulose tolerance tests of liver function were frequently,<sup>265</sup> but not consistently, noted. Thomson suspected that a hepatic dysfunction might be induced by failure of some activating hormone of external origin. The fact that gout usually attacks men suggests some endocrine factor. But so far no direct evidence thereof has been found.<sup>265</sup>

The presence of an allergic factor was suggested again.<sup>136, 531, 1031</sup> Perhaps acute attacks are due to bacterial or food sensitivity: cited as evidence was the case of a patient whose attacks were provoked by cider but not by alcoholic beverages.<sup>359, 532</sup> Gouty patients, however, do not exhibit the usual types of allergic reactions.<sup>359, 449</sup> Aschoff found no evidence that sensitization of articular or renal tissues exists in gout: "It is impossible to speak of an allergic inflammation in an attack of gout."

The infectious theory received no support: infections merely act as predisposing or provocative factors.<sup>265, 359</sup> The idea that gout results from hyperuricemia caused by some primary renal insufficiency also received no support.<sup>449, 938, 956</sup> Gout often causes, but does not result from, nephritis.

*Pathogenesis.* Gout must be regarded as a chronic disease; the arthritic attacks are merely its "acute explosions."<sup>408</sup> Hyperuricemia is one of the results, not the cause, of the disease. Is it due to (1) excess formation, (2) deficient excretion, or (3) diminished destruction of urates in the body? Modern writers favor the first idea.<sup>136, 938</sup> Talbott and Coombs found no evidence to support the second or third ideas. Indeed both during and between attacks several gouty patients (unless they had advanced renal damage) excreted more urates than did their nongouty controls. In gout most of the uric acid in human blood or other bodily fluids is either excreted or deposited, according to Talbott and Coombs, who stated that in this disease there is increased formation of uric acid. They continued the work of Talbott, Jacobson and Oberg<sup>3</sup> which indicates that many chemical changes besides those concerned with uric acid occur in gout.

Cyclic variations in urinary volume and content, in the body weight and in insensible loss of perspiration occurred among both gouty and nongouty persons but that of the gouty was of greater magnitude. In the latter, cyclic variations occurred during both the symptom-free periods and the arthritic attacks. Talbott and Coombs noted (as did His, 1899, and Fletcher, 1914) that prior to acute attacks a diminished urinary output of uric acid occurred; then about 24 to 72 hours before acute attacks diuresis with an increased concentration and excretion of various urinary constituents, especially sodium and chloride frequently occurred. This diuresis continued during the first few days of the arthritic attack, and was greatest usually just before or on the day of the greatest articular distress, at which time the output of fluid was about twice that prior to the diuresis and was accompanied by an increased excretion of urates. Subsequently as the cycle continued there was a diminished excretion of water, salt and urates. During the diuresis the patients paradoxically gained weight because of a significant reduction in their insensible loss of fluid. Gouty patients do not seem to be affected much by changes in weather and Talbott and Coombs noted no relationship between these clinical and chemical cycles and changes in external temperature and humidity, but they did note that a fall in barometric pressure practically always preceded diuresis by about 12 hours when there were no articular symptoms,

by about 12 to 24 hours when acute attacks occurred. The significance of these observations is not clear.

*Treatment of Acute Attacks.* The use of a brisk mercurial purge at the onset of the attack and a saline purge on alternate days during the attack was recommended.<sup>136, 956</sup> Compresses should be applied to the affected parts: either hot wet packs,<sup>956</sup> a cataplasm of kaolin, a lotion of soda bicarbonate, opium and belladonna,<sup>136</sup> or saturated solution of magnesium sulfate.<sup>195</sup> The most effective remedy is colchicum, given as the wine (15 to 20 minims every two to three hours) or as colchicine 1/120 or 1/100 grain every one to three hours until articular symptoms subside or gastrointestinal symptoms appear.<sup>106, 136, 603, 956</sup> Bowers gave colchicine 1/100 grain six to eight times daily for two to three days. Talbott and Coombs gave colchicine 1/120 grain every one or two hours for 8 to 16 doses depending on the patient's tolerance and the severity of the attack. The mechanism of the action of colchicine in gout is obscure and is not explained by the recent interesting studies of its cytotoxicologic effect.<sup>559, 582</sup>

Variable diets were used: a "purine-free diet,"<sup>956, 980</sup> a "soft diet"<sup>938</sup> or one which avoids foods rich in purine.<sup>603</sup> Cinchophen was not used by some,<sup>603</sup> used with due precaution by others in those cases in which salicylates<sup>359</sup> or colchicine<sup>956</sup> does not give relief, and then only if results of liver function tests are normal.<sup>136, 956</sup> On the days on which cinchophen was given, extra amounts of sugar and water,<sup>359</sup> and sufficient alkali to keep the urine faintly alkaline were prescribed: sodium bicarbonate 30 grains t.i.d.<sup>956</sup> or potassium bicarbonate 30 grains t.i.d.<sup>136</sup> Some approved the use of salicylates or aspirin when cinchophen was contraindicated<sup>136</sup> but others considered salicylates of doubtful value except as an analgesic.<sup>956</sup> The use of salicylates after the method of Jennings<sup>5</sup> failed to control the gout in two cases in which it was controlled later by cinchophen.<sup>359, 532</sup>

Crystalline thiamin chloride (vitamin B<sub>1</sub>) was given orally and parenterally (from 1 to 10 mg.; i.e., 330 to 3,300 international units daily) by Vorhaus and Kramer to 25 gouty patients. Despite the initial, acute exacerbations mentioned heretofore, it was given for from 3 to 36 months. Hyperuricemia was *not* controlled thereby; in some cases it increased, but "a definite change in the frequency and intensity of their disease" was noted. Results were marked in 11, moderate in 9, slight in 2, absent in 3 cases. This therapy has since been used by Kuhnau, Schroeder and Wolff (1937).

[One of us, W. B., was unable to corroborate these results.—Ed.]

Spa therapy is contraindicated during acute attacks,<sup>606, 955, 956</sup> but warm soda baths were considered excellent.<sup>980</sup>

*Interval Treatment to Prevent Attacks.* The occasional use of a mercurial purge and the frequent use of mild saline cathartics were approved.<sup>136</sup> In cases in which more than two attacks occurred yearly, colchicine, 1/120 grain t.i.d., was given for two or three days each week by some,<sup>136, 938</sup> for one

out of every four weeks by others.<sup>195</sup> Jacobson occasionally noted an apparent reduction in values for serum uric acid after use of colchicine, but because of great fluctuations in values for serum uric acid among untreated patients the effect of colchicine on hyperuricemia could not be determined finally. Others<sup>129</sup> accepted the older view that colchicine has no effect on uric acid in blood or urine and is powerless to avert attacks.

The intermittent use of cinchophen after the method of Graham (1927) was approved by Bower, but used by Cohen only for patients who did not tolerate colchicine (which he considered as effective a prophylactic as cinchophen). Cinchophen was considered more dangerous than valuable by others,<sup>603, 938</sup> but despite occasional danger Brown,<sup>129</sup> who was one of the first to describe cinchophen toxicity (1926), concluded that gouty patients should not be deprived of "its undoubted benefits." In lieu of cinchophen others prescribed 60 to 80 grains of aspirin daily for 4 days each week,<sup>603</sup> or neo-cinchophen 7½ grains t.i.d. for two days a week intermittently.<sup>408</sup> Aspirin seemed to reduce the level of serum uric acid occasionally.<sup>489</sup>

Dietary prescriptions varied considerably. Some<sup>489, 603, 938</sup> considered purine-low diets of unproved value and ineffective in controlling hyperuricemia at least when used for three months or less. Others regarded purine-free or purine-low diets effective if used long enough.<sup>135, 195, 221</sup> It was agreed that all alcoholic beverages including beer and in some cases cider also should be avoided.<sup>135, 136, 956</sup>

Many gouty patients are convinced that an annual or semi-annual visit to a favorite spa constitutes an effective prophylaxis against acute attacks.<sup>18, 19, 136</sup> Spa therapy was considered strictly contraindicated in acute attacks, but of value to gouty patients with little or no articular symptoms. The mild forms of hydrotherapy (vapor baths, brine baths) were considered safe but other forms must be avoided or used with caution lest they provoke acute attacks, "bath reactions" or "cure-crises."<sup>43, 606, 955, 956</sup>

*Additional Treatment.* Infected foci should be removed (for other than local reasons) in cases in which acute infections therein appear to provoke attacks of gout.<sup>334</sup> Occasionally it is easier to control a case of gout when some infected focus is removed.<sup>136</sup> For chronic gouty arthritis roentgen therapy or<sup>511, 1016</sup> ionization with lithium iodide<sup>44</sup> was recommended. [No results given.—Ed.] Excellent healing almost always results when ulcerating tophaceous deposits are adequately curetted.<sup>359</sup>

*Prognosis.* Gout was called a wretched, but tiny error of metabolism, not fatal to life (Van Breemen). Once the disease is present, it persists throughout life. There is no cure for it (Buckley; Talbott and Coombs). Some<sup>603</sup> are doubtful if any regimen materially affects the course of the disease, alters its relentless progress, or prevents acute attacks. An annual exacerbation of gout is to be expected, according to O'Reilly.<sup>728</sup> But most physicians have concluded that constant treatment accomplishes much in providing symptomatic relief and modifying the number and severity of

attacks.<sup>136, 938</sup> Some of Cohen's patients who had had frequent, repeated attacks for years, remained free of attacks for as long as seven years when they kept on their regimen.

### CINCHOPHEN TOXICITY

Between 1913 and 1935, 190 cases (107 nonfatal, 83 fatal) of toxemia from cinchophen or its derivatives were reported throughout the world. A survey of these cases by Bryce<sup>133</sup> indicated that persons over 40 years of age are more susceptible to toxic reactions than those younger, and that females are affected more frequently and have a smaller chance of recovery than males. In view of the quantities of phenylcinchoninates consumed throughout the world Bryce<sup>134</sup> considered cinchophen intoxication comparatively rare, and the frequency of fatal acute hepatitis from these drugs "extremely low."<sup>132</sup> According to his estimate the *minimal* empiric chance of *any toxic reaction* from a single dose of cinchophen or neocinchophen is about 1 in 7,500,000; and that of *fatal intoxication* from a single dose is about 1 in 15,000,000. Similarly he estimated that the *maximal* empiric chance of *fatal intoxication* is about 1 in 60,000; that of *any intoxication* is about 1 in 30,000. Bryce concluded that somewhere between these extremes lies the "true" figure representing the empiric chance of intoxication.

[Deaths from cinchophen toxicity reported in the literature probably represent only a fraction of the actual number that have occurred. Therefore it is not possible to say how correct Bryce's estimate is.—Ed.]

Sugg also admitted that minor forms of cinchophen toxemia affect only a small percentage, and fatal intoxication affects only a fraction of 1 per cent of those who use it, as far as reported cases are concerned, but he expressed the belief that many cases, even fatal ones, go unreported and the condition goes unrecognized because physicians are still not sufficiently aware of the dangers of cinchophen and related compounds. Especially are they unaware of the fact that delayed or acquired sensitivity can occur; hepatic injury therefrom can first manifest itself many months after use of the drug has been discontinued. From the literature Sugg collected 26 cases, to which he added six, in which no toxic reaction occurred when the drugs were first given, even in large doses for long periods, but in which toxic reactions accompanied or followed later courses of the drugs. Cutaneous reactions affected 12 patients, 2 fatally; hepatic reactions affected 22 patients, 12 fatally.

The mechanism of such toxic reactions in humans is unknown. They may be due to allergy of the liver, or to the superimposition of the choleric action of cinchophen on present or previous liver damage.<sup>134, 928</sup> The continued administration of cinchophen to dogs produces a chronic gastric ulcer similar in appearance and situation to human gastric ulcers; but no such ulcerous formation occurs in man (Bollman, Stalker and Mann; Simonds).

## THE URIC ACID PROBLEM

Certain amino acids, pyruvic acid, and glucose increase the excretion of uric acid; fats decrease it. Insulin increases the output of allantoin in dogs; it also increases the concentration of uric acid in blood and urine in Dalmatian hounds, but not their urinary allantoin. This is probably due to the mobilization of adrenalin by insulin: injections of adrenalin increase the uric acid content of blood and urine in Dalmatian hounds (Larson and Chaikoff, 1935). These studies were extended by Miller and Kuyper. The injection of insulin or adrenalin into rabbits increased the excretion of uric acid. Insulin apparently exerted its effect indirectly by lowering the blood sugar and causing mobilization of adrenalin. Adrenalin appeared to affect purine metabolism first, but protein catabolism as a whole may also be stimulated. The administration of 30 to 40 units of insulin to a normal person and to three diabetics produced no significant changes in uric acid content of blood or urine; neither did injections of 0.5 to 1 mg. of adrenalin. But when Rosenberg gave larger doses (65 to 100 units) of insulin to nine men, marked reduction in the level of blood uric acid occurred; the reduction in some cases amounted to 50 per cent or more. For example the level of uric acid of whole blood of one patient, given 100 units, fell from 2 to 1.3, that of plasma from 4 to 2.3 and that of serum from 5.4 to 1 mg. per cent. No urinary studies were reported. The decrease in blood uric acid was independent of the appearance of hypoglycemia: it occurred when hypoglycemia was permitted to develop and also when it was prevented from occurring by the administration of carbohydrate.

[Further work will be necessary to determine whether these studies can be applied to the problem of gout. The effect of insulin on blood uric acid was transient; values returned to normal within about six hours. The doses, given by Rosenberg mainly to schizophrenics, were larger than those generally given to diabetics. But these studies are of interest in connection with the case reported by Rabinowitch (1928) in which acute gout was repeatedly precipitated by injections of insulin, the only case of the kind we know of.—Ed.]

The uric acid content of blood and urine in Bright's disease was studied by Brøchner-Mortensen. The clearance of uric acid was compared to that of urea and creatinine. Despite significant renal insufficiency uric acid clearance was often normal. Usually retention of uric acid occurred only after considerable retention of urea; in severe cases the retention of urea was relatively much greater than that of uric acid.

[This is further evidence against the notion that gout may be a symptom of early nephritis.—Ed.]

To determine the "true uric acid" content of blood Blaich and Koch made determinations on plain serum and on similar serum after incubation with the enzyme uricase (from ox kidney) which specifically destroys uric acid. The difference in the two values was regarded as the "true uric acid." The average value of uric acid in 25 samples of human blood was 3 mg. per

cent before treatment, and 0.8 mg. per cent after treatment with uricase. Hence the true value of uric acid was 2.2 mg. per cent.

The purine metabolism of Dalmatian coach hounds was studied by Young, Conway and Crandall. Variations in the protein, amino acid and purine contents of their diets caused considerable variation in the output of allantoin but little change in that of uric acid. Apparently formation of uric acid in these animals is almost entirely endogenous and independent of the diet. The dietary purine is converted to allantoin and excreted as such. By studying the offspring of Dalmatian hounds ("high uric acid excretors") mated with collies ("low uric acid excretors") Trimble and Keeler noted that "high uric acid excretion" is inherited as an almost completely recessive, nonsex-linked character, dependent for its expression on the presence of a single pair of mendelizing genes. The genes underlying the "high uric acid excretion" and those underlying the production of Dalmatian spotting are resident in independent pairs of chromosomes.

[Such studies could and should be carried out on gouty families, particularly on the offspring of the union of a gouty and a nongouty person. Children and other relatives of patients with gout may demonstrate notable hyperuricemia without (other) symptoms of gout, according to Folin and Denis, 1915, and Jacobson.—Ed.]

#### PSORIASIS AND PSORIATIC ARTHRITIS

It has been stated, among others by Hunt,<sup>1</sup> that patients with chronic rheumatic diseases frequently exhibit psoriasis. In further studies Hunt noted a family history of various rheumatic manifestations in 70 per cent of 75 cases of psoriasis. According to her the following features characterized the supposed relationship between psoriasis and "rheumatic infections": (1) eruption on the skin following the appearance of rheumatic infection after "a latent period of some weeks," (2) a distinctive eruption, widespread guttate and nummular lesions resembling a secondary syphilid, (3) immunity in later life from the more serious rheumatic complications such as valvulitis. In contrast to Hunt's views Pringle considered the co-existence of psoriasis and rheumatic diseases uncommon. Among 2000 consecutive cases of "rheumatic disease" psoriasis occurred in only 17; of these 17 patients one had "subacute rheumatism," four had fibrositis, six had atrophic arthritis, three had hypertrophic arthritis, and three had "chronic villous arthritis." Among an additional 500 patients with rheumatism only three had psoriasis, making the incidence of psoriasis among 2500 rheumatic cases only 20 (0.8 per cent).

Two different relationships between psoriasis and rheumatism were cited by Barber: that in which the two were concurrently associated, and that in which the two conditions alternated. He stated that he had met several psoriatics who refused treatment for their eruption because its disappearance left them crippled with rheumatism. He regarded psoriasis as common in atrophic arthritis: "Of course psoriasis is so common a disease that its fortuitous occurrence with arthritis and other rheumatic disorders might be expected." But the association is "too frequent to be a coincidence." The special association, "psoriatic arthropathy," was considered by him "a well-



defined syndrome" characterized especially by the peculiar tendency for involvement of terminal phalangeal joints of fingers and toes with psoriasis of adjacent nails [a point of diagnostic importance previously described by one of us, P. S. H.<sup>3</sup>—Ed.] Also, according to Barber, in psoriatic arthritis, the progression of the articular lesions is generally less rapid, less continuous, and less relentless than in nonpsoriatic arthritis, so that despite some years of the former disease articular deformities and crippling may be slight.

There were 26 cases of psoriasis among about 1000 cases of atrophic arthritis (an incidence of 2.6 per cent) but only three cases of psoriasis among more than 1000 cases of hypertrophic arthritis studied by Dawson and Tyson. Hence the association of psoriasis with atrophic arthritis was considered "of real significance." The term, "psoriatic arthritis," has been applied by some workers to the combination of psoriasis with almost any form of rheumatism, and by others to the association of psoriasis with atrophic arthritis. Still others have used the term in a much more restricted and special sense to describe, not psoriasis with atrophic arthritis, but a form with characteristics which set it apart, perhaps, as a specific entity. Of the 26 cases of psoriasis and atrophic-like arthritis seen by Dawson and Tyson 12 were listed as "classical psoriatic arthritis" with features unusual for true atrophic arthritis but supposedly characteristic of psoriatic arthritis (involvement of terminal phalangeal joints in six, psoriatic nails in eight, asymmetrical arthritis—isolated joints being involved apparently at random—a relationship between the onset and activity of the skin and articular lesions which was fairly close in some, less close in others). Eight of the 26 cases were regarded as less typical examples of psoriatic arthritis, in general resembling ordinary atrophic arthritis and exhibiting no involvement of terminal phalangeal joints. The remaining six cases were regarded as cases of typical atrophic arthritis with coincident psoriasis. Because they could draw no sharp line of distinction between the three groups Dawson and Tyson regarded psoriatic arthritis as still an uncertain entity.

Two of Hench's patients with psoriatic arthritis were markedly relieved of their articular symptoms during pregnancy,<sup>481</sup> but pregnancy was listed by Ingram as one of the precipitating factors of acute psoriasis.

[These various reports reveal the confusion that exists about this supposed entity, and some of them increase rather than lessen the confusion. The question as to whether psoriasis is frequently associated with a variety of rheumatic diseases must be kept distinct from that as to whether a special form of arthritis with psoriasis exists which is distinctive enough to be called "psoriatic arthritis" rather than "atrophic arthritis with psoriasis." In neither of her papers (1933, 1938) did Hunt describe anything resembling the symptom-complex to which some restrict the term "psoriatic arthritis." Much more work must be done before the clinical boundaries of "psoriatic arthritis" can be drawn (if ever) with final accuracy. Meanwhile, three of us accept the entity, the others do not.—Ed.]

Because terminal phalangeal joints are frequently affected in association with psoriasis of adjacent nails physicians should distinguish psoriasis of nails from other ungual lesions. Ingram considered it impossible for one to diagnose psoriasis of the nails without the presence of psoriasis elsewhere. But Crawford and White con-

sidered the psoriatic nail lesions distinctive enough for recognition. Of Crawford's 231 cases of psoriasis 50 per cent presented psoriasis of nails. Fingernails were affected almost twice as often as toenails. The latter were never affected without lesions of fingernails. The principal changes in nails seen, in order of frequency, were pitting, changes in the color of the nail plate (present in about 66 per cent of 1277 affected nails), thickening of the nail plate, longitudinal ridging and erosion. The histologic picture was analogous to that of epidermal psoriasis. According to White psoriasis can occur in the nails alone, and the order of appearance of the nail changes in his cases was: (1) detachment of the nail, (2) partial parenchymatous alterations likely to end in partial destruction of the nail, (3) color changes, (4) shortening of the nail, (5) nail puncta. "The existence of these psoriatic erosions proves incontestably that psoriasis is a disease of internal origin and that the causal agent begins to multiply at the nail matrix, led there when the psoriasis passes into the erythrodermic phase and attacks the fingers. . . . Transverse lines appear and these usually indicate the initial onset of generalized psoriasis."

[No mention of articular lesions in joints adjacent to affected nails was made by Ingram, Crawford, or White.—Ed.]

*Etiology.* Theories on the etiology of psoriasis were discussed. According to Ingram there is no evidence that psoriasis is an infection, and very little to support the recent German view that it is due to a disturbance of fat metabolism. Reiss concluded that there was a decreased excretion of vitamin C in psoriasis from the disturbed cellular metabolism of the epidermis.

*Treatment.* No comments on the treatment of psoriatic arthritis were given, but control of psoriasis of skin and nails has been considered of first importance. The relative value of various remedies was discussed: for nails roentgen therapy and doses of arsenic (internally) alone or in combination<sup>1028</sup>; for the skin tar baths and artificial sunlight or cignolin inunction, protein shock, occasionally chrysotherapy.<sup>463</sup> Despite the vitamin C deficiency noted by Reiss the administration of vitamin C (redoxon) caused improvement in only two of his 13 cases of psoriasis (joints not mentioned). Injections of thorium X given "with great prudence," were considered useful (Weil and Bach). Following the work of others<sup>4, 5</sup> Brunsting used massive doses (average 300,000 units) of vitamin D (ertron), daily for 1.5 to 7 months. Two of 19 patients so treated had associated arthritis [but it was not materially benefited.—Ed.]. The psoriasis cleared entirely in three, was markedly improved in seven cases, was not significantly benefited in the rest. In three cases nausea and headache occurred; in none was there marked hypercalcemia. The results were "encouraging" but less striking than those reported by Cedar and Zon<sup>5</sup> who used crystalline vitamin D. Perhaps some forms are more potent than others.

#### HEMOPHILIA AND HEMOPHILIC ARTHRITIS

No articles on hemophilic arthritis appeared.

Further studies on the use of extracts from fresh normal serum and from placenta, both of which contain coagulation-promoting substances related to protein, were reported by Bendien and Van Creveld, and by Pohle and Taylor. Three patients

with hemophilia were treated by venesection with results "surprising" to Lawson and Graybeal who felt that possibly the hemorrhagic crises were an effort of nature for relief. For seven years, in one case, about 500 c.c. of blood were removed every 6 or 8 weeks or whenever fullness in the head or pains in joints appeared.

### ALLERGIC ARTHRITIS

In the usual vague way "allergy" was blamed for chronic polyarthritis. According to Keating "there are allergic joints, as there are allergic chests, intestinal tracts and other mucous membranes. Many patients have acute arthritic symptoms only following the ingestion of certain foods. . . . Arthritis frequently has a primary metabolic or endocrine basis upon which may be superimposed allergic manifestations to certain bacterial toxins or foods." The features of this so-called allergic type of arthritis were presumed to be the following: the joint symptoms are mildly progressive in type but occasionally become very acute. The spine as well as some of the larger joints is affected. Exacerbations are of short duration and are accompanied by mild gastrointestinal symptoms. Hydrops is not uncommon. Roentgenograms in early cases do not reveal any abnormality but later frequently reveal "changes suggestive of a mixed atrophic and hypertrophic type." [It would be difficult to identify "allergic arthritis" from this description. No clinical or pathologic proof of such an entity was given.—Ed.] Already mentioned was the report of Pottenger who stated that patients with atrophic and hypertrophic arthritis possess a hereditary tendency to allergy, exhibit food sensitivity in 90 per cent of cases, and "almost universally" manifest specific sensitization in various tissues. "The type of reaction in the joint suggests an allergic reaction."

In determining whether a disease belongs in the allergic group Gutmann applied these criteria: (1) determination of the suspected allergen by the skin test or the Prausnitz-Kuestner test (passive transfer of sensitivity), (2) disappearance of the symptoms when the allergen is removed, (3) re-appearance of symptoms following re-exposure to the allergen. Omitting the so-called infectious-allergic conditions (rheumatic fever, arthritis with tuberculosis and other infectious diseases), Gutmann recognized the following "allergic arthropathies": (1) genuine allergic arthritis, (2) joint swellings in serum disease, (3) "hydrops articulorum intermittens, angioneurotic edema fugax of Quincke," (4) "peri-arthritis, tendovaginitis," (5) purpura, (6) "gout, arthritis urica, psoriasis," (7) "rheumatism." He considered true allergic arthritis a "relatively rare" disease and cited two cases.

In case 1 a patient who had previously had "gall-bladder inflammation" (severe pain, vomiting, no fever or abnormality visible in roentgenograms) had repeated episodes of urticaria which disappeared when wheat flour and fish were avoided. Later after eating toast (wheat flour) and a salad containing fish she had pain in the region of the gall-bladder, itching of the entire body "without urticaria" and excruciating pain with swelling of a knee joint, but no fever. The red, swollen, painful knee required splinting. "It could be demonstrated that the eating of fish was the cause of the gall-bladder and knee joint symptoms, and that following the ingestion of wheat

flour urticaria occurred." [But the writer just said that itching occurred without urticaria.—Ed.] "However, while the urticaria and the gall-bladder symptoms quickly receded, the inflammatory condition of the knee joint continued for several weeks before it finally disappeared. The most striking proof of the allergic nature of the arthritis was the effect of eating fish."

In case 2 the patient had frequent short attacks of pain in the back, torticollis and lumbago. Later "spondylitis deformans" and intolerance to certain foods, nausea after eating boiled eggs, and diarrhea after drinking milk developed. "Allergy tests" revealed hypersensitivity to milk but not to butter, eggs or tobacco. Pains "definitely decreased" when milk, tobacco and eggs were avoided, later were intensified when milk and tobacco were allowed. "Milk and tobacco were again withdrawn and the pains decreased. As a result the spine became more mobile. Definite and continued improvement was evident after about one year."

Gutmann also cited two cases reported by Adelsberger and Munter (reference not given) caused by eggs and meat, and the case of Lewin and Taub<sup>4</sup> caused by English walnuts.

Examples of the other types of so-called allergic arthropathies were also given.

[We are not opposed to the idea that certain probably rare forms of acute recurrent or chronic arthritis may represent allergic reactions to certain foods, but most of the case reports of allergic arthritis leave much to be desired. Important details are often omitted, particularly precise details about the condition of joints when the offending foods are given or withdrawn. So often the evidence is unconvincing that the articular lesions subsided with significant rapidity and completeness when the offending antigen was avoided, and the clinical distinction between "allergic arthritis" and the ordinary forms is generally vague. Photographs and roentgenograms of the joints should be published; needed most of all are studies on the pathology of the condition.—Ed.]

#### "METABOLIC ARTHRITIS"

This term was not used in the literature under review.

#### ENDOCRINE ARTHRITIS

*Menopausal Rheumatism, Arthralgia and Arthritis.* Of 1000 women suffering from various menopausal symptoms 24 per cent complained of rheumatic pains ("arthritis and fibrositis").<sup>222a</sup> Long debated has been the question as to whether the menopause merely acts as a predisposing factor to the development, late in life, of any one of several common forms of arthritis, whether it can be the direct cause of such forms as atrophic or hypertrophic arthritis or whether it is responsible for a special type of true menopausal arthritis different clinically and pathologically from all others. For years "villous arthritis" has been offered as the true menopausal or climacteric arthritis. But since there has been no agreement as to the clinical or pathologic picture of menopausal arthritis and no experimental or clinical proof that any glandular dysfunction alone can cause arthritis, American physicians have in general refused to accept any form of menopausal rheumatism. According to present concepts the characteristics of the menopause are sup-

posedly (1) cessation of estrin secretion, (2) then overactivity of the anterior pituitary gland resulting in a flooding of the body by excess prolactin, (3) coincident overactivity of the thyroid gland and adrenal medulla. In some women the normal endocrine balance is upset less violently by the menopause and a new balance is established more readily than in others. It has been suggested that sometimes the menopause is characterized by pituitary failure, not pituitary stimulation (Hall) and by a deficiency, not an overactivity, of thyroid (Stone). Thus there may be more than one type of menopause, and if so there may be more than one type of menopausal rheumatism.

[The differences in menopausal biochemistry are probably more quantitative than qualitative.—Ed.]

Those who accept the idea that the menopause is related to one or more joint disturbances have conceived of the following possibilities. By acting as a predisposing factor the menopause may be the *indirect* cause of any one of several common forms of rheumatism including atrophic or hypertrophic arthritis and fibrositis, or the menopause may be the *direct* cause of a variety of forms of menopausal rheumatism such as the following: (1) polyarticular hypertrophic arthritis ("menopausal hypertrophic arthritis") presumably due to the thyroid deficiency of the menopause, (2) polyarticular atrophic arthritis ("menopausal atrophic arthritis"), (3) polyarthralgia ("menopausal arthralgia"; stiff, sore joints with or without mild subcutaneous edema, but not a true arthritis) presumably due to a deficiency, not of thyroid, but of ovarian secretion, (4) menopausal fibrositis (stiff, sore muscles; tender subcutaneous fibrofatty nodules), (5) "villous arthritis," a special form of arthritis with distinctive pathologic reactions confined almost exclusively to knees.

1. "Menopausal arthralgia." The characteristics of this condition as seen by Hall in 53 cases included: freedom from joint symptoms until after artificial menopause; then the appearance of joint pain, stiffness and tenderness with no true articular swelling but with slight subcutaneous edema, full motion and no deformity; generally normal sedimentation rates; occasionally low metabolic rates; *aggravation* of menopausal symptoms by thyroid therapy; relief of menopausal symptoms and joint pains with adequate doses of estrogenic substance; return of joint pains when estrogenic substance was discontinued or substituted by a placebo. The articular symptoms were worse after rest and sleeping, better after moderate, but worse after excessive, physical activity. Thus some might call the condition periarticular fibrositis. Coincident hypertrophic arthritis affected one-third of Hall's patients. No pathologic studies were made but the disturbance was believed to be, not a true arthritis, but one in periarticular tissues. In some cases pain was chronic and mild or moderately intense; in others it was severe and spasmodic, perhaps from vascular spasm.

Treatment. Intramuscular injections of progynon B were given twice weekly; doses varied considerably and failures were usually due to inadequate

dosage; as a rule 10,000 international (2000 rat) units were sufficient if continued at least four to six weeks, but in some cases 50,000 international (10,000 rat) units were required. Single doses were rarely effective; generally no effect was noted until after three to six weeks of treatment. Of the 53 patients so treated 40 were "adequately treated"; of them 80 per cent were materially ("50 to 100 per cent") relieved of their menopausal and articular symptoms; 70 per cent responded in "striking and often dramatic fashion, obtaining almost complete relief." Including those "inadequately treated" 66 per cent of the total 53 patients were "helped" by estrogenic therapy.

2. "Menopausal atrophic and hypertrophic arthritis." Hall also noted 18 "castrates" who were well until castration and then, coincident with the onset of menopausal symptoms, developed unquestioned atrophic or hypertrophic arthritis as well as "arthralgia." "Because of the history, because no other cause could be found for the arthritis, and because the menopausal symptoms and arthralgias yielded to estrogenic therapy, one is tempted to conclude that castration or the removal of the internal secretions of the ovaries may be a direct or indirect cause of true arthritis. No such conclusion can be drawn on the evidence so far collected."

The studies of Gardner and Pfeiffer are of interest in this connection. Mice were injected weekly with comparatively large amounts (100 to 1000 international units) of estrogen (hydroxy-estrin benzoate) over long periods of time up to 348 days. There occurred an extensive resorption of parts of the pubic and ischial bones, and replacement of the pubic symphysis by an interpubic ligament; but elsewhere there was marked condensation of bone and replacement of marrow cavities with endosteal bone.

3. "Villous or climacteric arthritis." Current descriptions of this supposed entity continued to vary somewhat.<sup>583, 723, 808, 917, 954</sup> Its proponents consider it to be a distinctive clinical and pathologic syndrome; it is *not* atrophic or hypertrophic arthritis at the menopause. The French call it "lipoarthrite seche." It almost exclusively affects the knees of women (usually obese) at or near their natural or artificial menopause (Stone). According to others it may also affect other weight-bearing joints (hips, ankles—Robinson), the back (Oldershaw), occasionally wrists and thumbs (Thomson). Symptoms are aching stiffness of joints, mostly of knees, relieved by rest. Tenderness is confined to the involved parts of synovial membrane and is found mostly at the inner aspect of knees at the attachment of the internal lateral ligament to the internal femoral condyle.<sup>583, 917</sup> Pain and tenderness are "less severe than in atrophic arthritis." There is some "swelling" generally at the inner side of the knee joint. This swelling is due to periarticular fat pads, and to the enlarged synovia.<sup>808, 917</sup> Synovial effusion is not present according to Stone, but according to Robinson it is sometimes present due to trauma from pinching of the swollen synovial villi. According to Stone there is no restriction of articular motion; indeed mobility may be abnormally increased due to laxity of ligaments. But according

to Little joints are enlarged, tender and limited in motion in severe cases, but the periarticular changes and limited motion are never as severe in this disease as they are in atrophic arthritis. Common associated conditions are obesity and flat feet.

Roentgenograms of knee joints are negative except for the appearance of "small punched out areas behind the articular cartilage" with some bony decalcification from disuse, according to Little; they are negative in early stages, but may reveal secondary hypertrophic arthritis later in the disease, according to others.<sup>808, 917</sup> Robinson stated that "clinically and radiologically menopausal arthritis is identical with osteoarthritis," yet he insisted that it must be carefully differentiated therefrom.

[He did not clearly show how this could be done.—Ed.]

The distinctive articular pathology of villous arthritis was again said to be a "peculiar hypertrophic change" in synovial membrane (Thomson) with production of villous hypertrophy extensive enough to be palpable in severe cases (Little). There is no true arthritis, according to Stone; there is synovial hyperemia but no inflammation of the membrane. The fatty synovial fringes and villi increase in size and number, sometimes to the extent that the joint is packed with fatty arborescent growths, the branched villous processes insinuating themselves between patella and condyles and between condyles and semilunar cartilages with resultant pinching thereof. Fat in the posterior pouch of the knee is also increased (Stone).

[None of these writers presented photomicrographs of these pathologic reactions; they apparently relied on the published descriptions of others. If they have original material, it would be very helpful if they published it. We know of no one, certainly not in recent years, who has presented photomicrographic evidence clearly showing the pathologic specificity of villous arthritis with its differentiation from atrophic, hypertrophic and other common arthritides. No such entity is described in the standard works on articular pathology (Strangeways, 1905 et seq.; Nichols and Richardson, 1909; Pommer, 1913; Knaggs, 1926; Allison and Ghormley, 1931). The chronic villous polyarthritis of Schüller was classified by Stockman, 1920, under chronic infectious arthritis, in contrast to rheumatoid arthritis. We would appreciate receiving original references on the pathology of menopausal villous arthritis.—Ed.]

**Etiology.** The cause of the disease was variously considered to be a thyroid deficiency occurring at the menopause (Stone), primarily metabolic changes including thyroid deficiency, secondarily trauma (Thomson), a temporary ovarian insufficiency (Oldershaw). But no data concerning metabolic rates or hormone assays were given.

**Treatment.** Remedies recommended were reduction of obesity, mild hyperpyrexia with foam baths "to start weight reduction" (Stone), thyroid extract—"the sheet-anchor of treatment" used not only for its weight reducing effect but as replacement therapy (Stone; Thomson), rest and heat for affected joints ("exercise is bad" for these joints), use of a device to limit articular motion to prevent trauma to hypertrophied villi (Little), weekly injections of estrogenic material, faradic current to increase muscle tone even though the patient is resting, hydrotherapy "to increase metabolic

activity" (Thomson). Little performed synovectomy in intractable cases: "it may give relief for years"; in old severe cases he considered arthrodesis sometimes necessary. Oldershaw and Robinson used intrapelvic diathermy "to accelerate the endocrine activity of the ovaries." [No hormone assays were made to support this statement.—Ed.] Such treatments presumably arrested the arthritis in a relatively short time. If the disease is left untreated "osteoarthritis inevitably supervenes after a number of years. But here at least is one variety of preventable osteoarthritis; if treatment is undertaken thoroughly, most of these 'menopausal knees' get well" (Stone).

A general discussion of the use of estrin in the treatment of "chronic rheumatism" was given by Cawadias.

4. "Menopausal fibrositis." This was said to affect obese women at the menopause with signs of hypothyroidism. Reported features were mild myxedema, variously situated subcutaneous fat pads, and subcutaneous nodules which are sometimes very painful and tender but which on excision reveal only simple lipomas without signs of inflammation. Robinson used diathermy and deep massage to the nodules, and intrapelvic diathermy twice a week for one or two months; he stated that most cases were relieved thereby.

[No pathologic or biochemical studies were given to support these statements.—Ed.]

*Juvenile Hip Disease from Hypothyroidism.* A disturbance of ossification of the capital epiphysis of the femur in hypothyroid children was described by Benjamin and Miller. Two types of maldevelopment may arise: (1) one involving the epiphyseal plate may produce epiphyseal slipping; (2) the other produces osteochondrosis of the femoral head. Coxa vara may develop later.

*Joints and the Parathyroids.* Diseases of the parathyroids produce no known articular disease. Degenerative muscular lesions but no articular changes were noted by Cantarow, Steward and Housel in dogs with experimental acute hyperparathyroidism. Many patients with hyperparathyroidism, however, experience skeletal aches and pains which they call "rheumatism." The pain is usually localized to muscles and bones but sometimes to joints. In recent cases patients experienced "pains in arms and knees,"<sup>297</sup> tingling pain in hands and feet, stiffness in legs,<sup>608</sup> pain and lameness in a hip,<sup>345</sup> stiffness, pain and aching in extremities,<sup>900</sup> weakness, fatigability, muscular hypotonicity and ligamentous relaxation.<sup>901</sup> Diagnosis becomes clear when the proper biochemical and roentgenologic studies are made.<sup>327, 362, 496, 1003</sup> The disease should not be confused with arthritis.

#### MISCELLANEOUS DISEASES OF JOINTS

*Pharmaceutic Arthralgia: "Chemical Arthritis."* While taking certain drugs (e.g., thyroid extract, excess amounts of soda bicarbonate, bismuth) patients may note pain in muscles or joints sometimes called myalgia or



arthralgia medicamentosa, medicinal arthralgia, "paratherapeutic articular disturbance."<sup>4</sup> To this list O'Connor added lead, arsenic, radium and insulin (a biologic product, not a drug) as occasional causes of "toxic arthritis."

[No true arthritis occurs.—Ed.]

*Intermittent Hydrarthrosis.* Prolonged remissions of this disease may occur spontaneously, as a result of certain remedies, or during certain conditions such as pregnancy. Marked relief during pregnancy was noted by Hench in one case and he cited other cases previously reported. Swett advised synovectomy for the disease.

*Synovitis.* A patient with mild acute traumatic synovitis later slowly developed what Swett called "synovitis ossificans." Roentgenograms revealed extensive infiltration of synovia with actual bone. The membrane was removed, its pathology described.

*Synovioma.* This is a rare condition.<sup>5</sup> Clinical and pathologic data in a new case were reported. The swelling was behind the knee of a young man. After amputation of the leg the patient responded well.<sup>166</sup>

*Synovial (Baker's) Cyst of the Knee: Posterior Synovial Herniation.* Any cystic swelling about the knee in which the cyst has a cellular lining which simulates synovial membrane is a Baker's (1877, 1885) cyst. To be distinguished are a synovial "cyst" in the popliteal region resulting from posterior herniation of the synovial membrane of the knee joint, and the swelling caused by hyperplasia and inflammation of one of the posterior bursae of the knee. Synovial cysts from posterior herniation of the knee joint originate beneath the medial head of the gastrocnemius muscle where there is a natural weakness in the posterior capsule of the knee joint. Usually the greater part of the swelling is distal to the transverse flexion crease on the skin. These cysts are most noticeable when the leg is extended; they are not especially tender, but may produce aching, sometimes severe sharp pain and occasionally intermittent effusion into the knee. There may be considerable interchange of fluid between the hernial sac and the knee, hence the effusions in each may vary in size. Treatment is to remove the hernial sac surgically and repair the opening in the joint capsule. Results in 11 cases were reported (Edmunds and Hebble; Haggart).

Of the 12 bursae around the knee joint two are placed posteriorly and one is between each head of the gastrocnemius muscle and the joint capsule. The one beneath the inner head of the gastrocnemius extends between this muscle and the semimembranosus muscle and is called the semimembranosus bursa. Either of these posterior bursae may be connected with the synovial cavity of the knee. If they are not, the effusion of a bursitis cannot be pressed anteriorly into the knee joint. If they are connected differentiation between bursitis and posterior synovial hernia is more difficult.<sup>401</sup>

*Tenosynovitis.* Gould cited the common types, "simple tenosynovitis," the infectious forms including gonorrheal and tuberculous, and stenosing tendovaginitis, and ganglion. There are two types of stenosing tendo-

vaginitis: (1) a strictly local thickening of a tendon sheath of a finger flexor opposite a metacarpophalangeal joint causing a "snap-finger"; it is treated by surgical removal of the local fibrosis; (2) stenosing tendovaginitis at the radial styloid process (deQuervain's disease). As a result of acute or chronic trauma there is chronic thickening of the sheaths of the extensor pollicis brevis and abductor pollicis longus. There may be much tenderness over the radial styloid process and an elongated swelling from hypertrophy of the annular ligament. About 250 cases have been described, mostly in women. Ten new cases were reported (Cotton, Morrison and Bradford; Keyes). Palliative treatment should be tried but is "mostly disappointing" (Gould). Operative treatment is simple and satisfactory, often dramatically so.

*Tenosynovitis Crepitans; Crepitating Peritendinitis.* Howard's summary of 32 cases was reported in our last Review. He has now studied 72 cases. Chiefly affected were the extensor muscles of wrist and thumb. The disease may be caused by trauma or by functional overactivity. Its clinical and pathologic features were again described. Massage, baking and diathermy are contraindicated. Treatment involves absolute rest in plaster splints. Duration of disability with adequate immobilization was 12 days, with partial immobilization 23 days.

*Ganglion.* Simple ganglion is usually a swelling resulting from the mucinous degeneration of a fibrotic change in a small portion of the wall of a tendon sheath.<sup>378</sup> It is annoying but rarely disabling. Its contents can rarely be aspirated. Treatment involves pressure dispersion or incision (technic given) but not dissection except in special cases.

*Osteochondritis.* Legg-Perthes' disease has been called "osteochondritis deformans juvenilis" of the hip. It was described by Legg and Waldenström (1909), later by Calve (1910) and Perthes. The cause is unknown. Waldenström preferred the term "coxa plana" and described the changes in serial roentgenograms made in four early cases. Conservative and not surgical treatment was advised. To the five cases previously reported Goldenberg added a sixth case in which Perthes' disease followed traumatic dislocation of the hip. Changes radiologically similar to Legg-Perthes' disease but pathologically different may affect the hips of juvenile cretins as a result of imperfect ossification secondary to hypothyroidism. Five cases were reported (Benjamin and Miller; Albright).

Five new cases of juvenile ischiopubic osteochondritis were also reported (Corper; McFadden).

*Arthropathy.* The more common forms of arthropathy were listed by Worster-Drought thus: (1) tabetic arthropathy (Charcot's disease) including the rare form, tabetic vertebral osteo-arthropathy; cases involving a knee, a wrist and a metacarpophalangeal joint were reported<sup>792, 1050</sup>; (2) arthropathy of syringomyelia; a case involving both wrists was reported, also two cases of Morvan's type of syringomyelic arthropathy (atrophy and disappearance of terminal phalanges of fingers) in one of which there were ex-

tensive changes in a shoulder<sup>613, 1050</sup>; (3) posthemiplegic arthropathy, first described by Alison (1847), usually affects a shoulder; (4) hypertrophic osteo-arthropathy. Most of the cases of the last type are related to chronic pulmonary disease, others to congenital and valvular heart disease and less often to chronic hepatitis or enteritis. No primary lesion is discovered in lungs or elsewhere in from 4 to 14 per cent of cases (Locke, 1915). One case secondary to pulmonary new growth was reported.<sup>1050</sup> In one case, reported in much detail, no primary cause was found (Campbell, Sacasa, Camp). A case of clubbed fingers and toes associated with a congenital pulmonary cyst was also noted.<sup>675</sup>

*Idiopathic Familial Generalized Osteophytosis.* This condition somewhat resembles either atypical acromegaly or hypertrophic osteo-arthropathy but is considered different from either. Also called "familial acromegalic-like skeletal disease" its features are onset of the disease at puberty, progression by exacerbations, marked chronicity, extreme bony change, absence of known primary disease, and the presence of a familial tendency. Freund reported a case in which the disease started as a hyperplastic process of several joints and simulated subacute recurring arthritis.

*Sclerodactylia.* Features of this condition are stiffness, atrophy, and deformity of fingers with tightening, ulceration and pigmentation of skin. Roentgenograms usually reveal phalangeal decalcification, resorption of phalanges at the finger tips, amorphous, calcareous granules in phalangeal soft tissues, interosseous calcareous nodules, and various arthritic changes, mainly atrophic. Two cases presumably related to scleroderma were described.<sup>376, 456</sup> Also reported was a most unusual case of progressive diffuse scleroderma with sclerodactylia and calcinosis in a child aged 12 years, sick for 10 years, and now looking like no human being, as the photographs show (Pachman).

*Hereditary Arthrodysplasia.* Sever reported a case of this condition best described by Turner (1933). Its features were: patellae placed not in the usual position but on the external aspect of both knees, limitation of supination of hands and of extension and flexion of both elbows, rudimentary thumb nails, other nails being normal. Roentgenograms revealed the lateral position of the patellae with newly formed, articular facets on the lateral condyle of the femurs, and at elbows multiple exostoses. Hereditary arthrodysplasia apparently is seen only with hereditary dystrophy of nails. Several of the patient's relatives had the latter but not the former. The condition, inherited and congenital, apparently is due to some defect in the closing or fusing of the ectodermal and mesodermal layers of the embryo.

*Arthrokataclasis: "Otto Pelvis."* This is an intrapelvic protrusion, a sinking in or subsidence of the acetabulum with protrusion of the femoral head through it, resulting in limitation of motion of the hip. Wardell saw the condition in one hip of a woman with atrophic polyarthritis who had fallen on her hip. A Smith-Petersen acetabuloplasty gave satisfactory results.

*Ehlers-Danlos' Syndrome.* Four cases were described.<sup>100, 788, 883, 1010</sup> Features were marked hypermobility of joints, excessive elasticity of skin, friability of skin and blood vessels, pseudotumors in the scars of lesions resulting therefrom, movable nontender subcutaneous spherules of fat in various regions.

*Deposits of Calcium or Bone About Joints.* It is often difficult to determine from roentgenograms whether these deposits are in tendons, ligaments, or bursae adjacent to joints. Milch and Green described several cases of calcification about the flexor carpi ulnaris tendon, with acute sharply localized pain and tenderness over the area around the pisiform bone, limited wrist motion, sometimes acute inflammation, and early subsidence of symptoms with the use of heat, immobilization and salicylates. It may be due to trauma. The deposits seemed to be in the tendon and not in peritendinous soft tissue or in the bursa subjacent to the flexor carpi ulnaris. Some of them disappeared under treatment. Buxton described "ossification" in the ligaments of the elbow from injury. One end of the ligament is torn from the bone and carries with it some periosteum; a hematoma results and bone cells are activated. Such a condition can be prevented by proper immobilization of the elbow after injury. Complete or partial absorption of deposits of bone in muscle may result from immobilization but as a rule "once bone is formed in ligament, it remains unchanged," probably because ligaments are too avascular to carry out the process of absorption.

[The writer spoke of "ossification" and deposits of bone, but no histologic evidence was given to indicate whether the deposits were of calcium salts (which may be rapidly reabsorbed) or true bone. One of us, A. J. K., believes they are true bone.—Ed.]

*Brodie's Abscess Producing Chronic Arthritis.* A boy with a swollen wrist was seen by Ray. The cause of the arthritis was an adjacent Brodie's abscess, a localized form of osteomyelitis.

*Cartilaginous Changes Due to Rickets.* Three cases of severe late rickets were studied at autopsy by Freund. Cartilage changes included edema and decomposition of hyaline ground substance, lack of cartilage calcification and enchondral ossification.

#### DISEASES OF BURSAE

Meyerding noted the common types and the surgical treatment of bursitis: traumatic bursitis from acute but more commonly from chronic trauma (e.g., "miner's elbow"—olecranon bursitis; "coachman's bursa" or "weaver's bottom"—ischial bursitis; "tennis elbow"—radiohumeral bursitis; "housemaid's knee," "nun's knee"—prepatellar bursitis), bursitis from nonspecific (rheumatic) or specific infections (e.g., tuberculous, syphilitic), and gouty bursitis. Commonest of all is the bursitis involved in a "bunion." Bursitis may occur not only in preformed bursae but also in newly formed bursae near bony prominences subject to injury.

*Acute Hematogenous Bursitis.* This condition may (rarely) arise in association with acute infections, septicemia, etc., and may cause chills, fever, prostration, and localized pain and swelling which may be mistaken for acute arthritis. Cooperman reported six cases: a subacromial bursa was affected in four cases; a gluteal in one and a prepatellar in one case. Diagnostic needling revealed pus and was followed by incision and drainage. Gluteal bursitis is often not diagnosed because it is difficult to know whether the hip joint or one of the 10 to 30 bursae in the buttock is affected.

*Popliteal Bursitis.* Already mentioned was posterior hernia of the synovia into the popliteal space which Haggart called "Baker's cysts," and its relationship to true bursal swellings from popliteal bursitis which Wilson, Eyre-Brook and Francis also spoke of as "popliteal cysts, Baker's cysts." [Obviously the term "Baker's cysts" has a different meaning for different writers.—Ed.] Wilson and his colleagues noted six primary bursae around the popliteal fossa and medial side of the knee, chief of which was the gastrocnemio-semimembranosus bursa. Its two parts are generally connected, hence the name. It frequently connects with the knee joint. Twenty-one popliteal cysts were removed at operation; most, if not all, of them were from fluid distention of the gastrocnemio-semimembranosus bursa, rather than synovial herniation. Although these cysts usually are connected with the knee joint (air injected into them passes promptly to the knee, as shown in roentgenograms), they usually remain distended despite attempts to empty their contents into the knee by pressure. This behavior suggests a valvelike action at the mouth of the cyst. It was believed that such cysts arise, not from infections or toxins but from injury to the bursal wall caused by single violent or repeated vigorous contractions of muscle which are followed by effusion. Operative excision was recommended: the cyst walls show blood pigment, fibrous thickening and cartilaginous and osteoid metaplasia.

*Iliopectineal Bursitis.* The iliopectineal bursa often connects with the hip joint. Inflammation of this bursa which occurs not infrequently, generally from trauma, is often undiagnosed. Finder reviewed the subject. Conservative treatment includes rest in bed and hot or cold compresses; aspiration will not cure the condition. Surgical excision, a tedious procedure, usually is recommended but Finder successfully treated a patient by surgical obliteration (closing the passage between bursa and hip, everting the walls of the sac and anchoring adjacent muscle fibers into its floor).

*Calcification of Epicondylar Bursa.* Hamilton saw a patient who clinically had severe "tennis-elbow": swelling, tenderness and heat about the external epicondyle of the humerus. In roentgenograms deposits of calcium on the radial side of the elbow were placed too laterally to be in the radial collateral ligament. Because the deposit of calcium was sharply defined and globular, it was thought to be in the bursa. A plaster splint was applied, later a cock-up splint. A month later symptoms and most of the calcium had disappeared.

"*Subdeltoid and Subacromial Bursitis.*" These will be discussed under the next heading.

#### DISEASES ABOUT THE SHOULDER JOINT: "THE PAINFUL SHOULDER"

Painful shoulders with varying degrees of stiffness are common. Some physicians blame them all on "subdeltoid bursitis"; others use the term "supraspinatus tendinitis" as their uniform diagnosis. Others realize that anatomically the shoulder joint is, like the back, a rather complex affair, and that like backache, a painful shoulder may result from a number of rather closely related and often overlapping syndromes. Each of these syndromes produces a somewhat similar symptom complex but each has its own distinguishing features. Various names have been given these syndromes: subdeltoid bursitis, subacromial bursitis, calcareous subdeltoid or subacromial bursitis, degenerating, calcified or ruptured supraspinatus tendinitis, Codman's syndrome, peritendinitis calcarea, scapulohumeral peri arthritis, Duplay's disease, "shoulder joint complex," "painful shoulder syndrome," "frozen shoulder," periarticular fibrositis, peri arthritis or "arthritis" of the shoulder joint. Some of these terms are synonymous but others are not. The different conditions may arise independently but more often they occur in definite relationship to each other. The structures involved, capsule, tendons and bursae of the shoulder, are so contiguous and functionally interdependent that disease in one may cause disease in another (Ferguson; Gray; Watson-Jones).

According to Codman (1934) "the subacromial, subdeltoid and subcoracoid bursa are one and the same thing, although films of tissue may separate them," depending on the anatomic position and also whether the arm is in abduction or rotation. The subacromial bursa (Codman's preferred term) has the deltoid muscle above it; its floor is formed by the fibrous tissue sheet composed of the fused tendons of the supraspinatus, infraspinatus, teres minor and subscapularis. Disease in these structures results sometimes from infection but more often from acute and chronic trauma.<sup>81, 279, 819, 827</sup> The bursa may be affected primarily, but is more often affected secondarily from disease in the musculotendinous cuff (especially the supraspinatus tendon and muscle) or in the bones of the shoulder joint. The deposits of calcium near the bursa were first thought to be within the bursa (Painter, 1907). It is now believed that they are usually not inside the bursal sac, not even within its walls, but in the region just beneath the bursa, generally in the tendon of the supraspinatus muscle near its insertion but sometimes in the tendon of the infraspinatus, subscapularis or teres minor.<sup>279, 662, 819, 827</sup> When deposits of calcium are present within the bursa they generally have ruptured into it from the underlying tendon (Rubert).

1. *Supraspinatus Tendinitis without Calcification.* The supraspinatus muscle and tendon are common sites of disease because the muscle is weak; its progenitor was designed to work with the force of gravity and swing the foreleg of quadrupeds

but in its human form it must work against gravity to raise the arm; it is attached close to the fulcrum of a long lever, and it can be pinched easily between the humerus and the acromion (Ellis). Being relatively avascular, the tendon commonly degenerates; an attrition lesion results from the metabolic change of age and trauma.<sup>819</sup> Symptoms of degenerative tendinitis include painful but not limited abduction with maximal tenderness at the greater tuberosity of the humerus where the tendon is inserted. Pain is most notable when the arm is being moved in abduction through the part of the arc between 60 and 120°. During this part of the arc the tendon impinges against the acromion process; abduction of more than 120° is painless as the tendon slips under the acromion process and there is no impingement or strain.<sup>1006</sup> Treatments used include diathermy, radiant heat or injections of 5 to 10 c.c. of 2 per cent procaine which may give great relief for five or six hours, sometimes much longer (Watson-Jones).

2. *Supraspinatus Tendinitis with Calcification.* Acute trauma may cause a muscle bruise with effusion of blood, a tear in some fibers of the tendon, or partial evulsion at its insertion. The blood in the hematoma is altered into an amorphous calcareous mass (calcium phosphate and carbonate) deposited "wholly within the tendon" <sup>1006</sup> under the bursal floor.<sup>279</sup> Thus the deposits of calcium in cases of "subacromial bursitis" result from slight tears in the supraspinatus tendon which nature has attempted to repair (Codman 1934; Outland and Shepherd). How often degeneration of the muscles and tendon precedes and predisposes to tears and how often the tears precede and cause localized degeneration is undetermined. The symptoms of supraspinatus tendinitis with and without calcification are about the same except for roentgenographic evidence of changes in the former. In acute cases pain and disability may be great.

Deposits in the supraspinatus tendon were compared to those occasionally seen in other tendons, e.g., about the wrist, elbow, knee or hip. In all these cases the same basic lesion and symptoms were present. Hence for them Sandström and Howard proposed the general term "peritendinitis calcarea." Among 320 cases studied by Sandström deposits were at shoulders in 259, hips in 48, elbows in 6, fingers in 6, knees in 5, toes in 3, wrists in 2 cases [a total of 329 cases as some patients had more than one deposit.—Ed.] Fever occurred in 70 of 80 cases in which temperature was taken; sedimentation rates were elevated in 70 of 75 cases. The disease occurred any time after the age of 10 years, but most often after the age of 40 or 50 years. In these 320 cases the calcium was partly in tendons, tendinous, capsular and ligamentous tissues, partly in periarticular and peritendinous connective tissue, only once in the wall of a bursa and never within a bursal sac. Additional pathologic reactions were necrotic changes in tendons, ligaments and joint capsules, marked vascular changes (hypertrophy of the media), and some regenerative processes. According to some <sup>1006</sup> the tooth-paste-like deposits of calcium may induce a secondary irritative hyperemia which may cause spontaneous resorption of the calcium and may also cure the underlying tendinitis. But deposits should not be removed surgically simply because they are present. The pain is due, not necessarily to the deposits of calcium, but to the lesions which foster them. In some cases an opposite symptomless shoulder may show as much or more deposit of calcium than the painful one. The deposits often disappear spontaneously, sometimes within a few days, or they may persist despite treatment which relieves all other signs and symptoms.

Conservative treatment, such as various types of physical therapy and rest, should be used first.<sup>81, 819</sup> Martucci preferred to use diathermy daily with the arm in a sling night and day for about two weeks; then massage and high frequency currents. The joint should not be fixed in plaster or it may "freeze." Some advised the use of an abduction splint.<sup>81, 279</sup> New abduction splints were described (Bettmann); particularly ingenious was that of Papurt in which a light leather cap is fitted with a ring and a wrist bracelet with a snap. The wrist is merely snapped to the cap after

it is on the head, and thus abduction is maintained. According to Watson-Jones in many such cases the shoulders cannot be supported in abduction as they are too painful. Acute pain may be relieved by injections of 20 c.c. of 1 per cent solution of procaine into and around the bursa.<sup>61,662</sup> For small deposits, diathermy, radiant heat and massage generally suffice. Troedsson noted disappearance of deposits in 13 of 30 cases after 6 to 45 hours of diathermy given within 3 to 11 weeks by a technic which he considered superior to others. Sandström considered roentgen therapy most satisfactory in both acute and chronic cases (technic given). Deposits of calcium often disappeared after two or three weeks, sometimes longer. Treatment for several months was necessary in some cases and deposits did not always disappear completely. [But many roentgenograms were published showing the disappearance of the deposits.—Ed.] Surgical evacuation of the deposits is necessary in some severe cases and may give immediate and complete relief (Watson-Jones). Meyerding recommended operation only if the deposits were associated with pain and other symptoms, and if conservative therapy was unsatisfactory. Manipulation of such painful stiff shoulders under anesthesia is sometimes successful but should be done with great care; Meyerding described the technic.

3. *Rupture of the Supraspinatus Tendon (Complete or Incomplete)*. When degeneration of the muscle and tendon has resulted from age and chronic trauma, very slight acute trauma is needed to injure them even further. Hence partial or complete rupture of the tendon is common among elderly people and those in certain occupations (painters, plasterers). It is found in from 17 to 30 per cent of cadavers (Keyes, 1935; Watson-Jones) and is considered by some<sup>279</sup> the commonest cause of painful shoulders among industrial workers. When the tendon is torn, the floor of the subacromial bursa is sometimes, but not always, torn with it, creating an opening between the bursa and the shoulder joint.<sup>741</sup> Symptoms and signs of incomplete tendinous rupture are rather similar to those of tendinitis: pain in the shoulder, sometimes referred to the insertion of the deltoid, tenderness at the greater tuberosity of the humerus, limited and painful internal rotation, abduction between 70 and 90° which is probably possible but very painful and associated with the characteristic "catch" of pain as the injured fibers pass the acromion.<sup>1006</sup> According to Ellis a partial rupture almost always heals but it may take six months. Treatment by heat and gentle motion was used; Ellis used a sling; others advised immobilization in abduction and external rotation for from three to six or eight weeks and surgical repair thereafter if relief is unsatisfactory.

Clinical signs of complete rupture include sudden onset of sharp pain, loss of power to abduct the arm, tenderness over the greater tuberosity<sup>741</sup> or at the tip and lateral aspect of the acromion<sup>279</sup> (some found Dawbarn's sign not very helpful),<sup>741</sup> undue prominence of the greater tuberosity because its tendinous covering is absent, a fine crepitus on palpation of the tuberosity as it moves under the acromion on passive motion of the arm. The "diagnostic sign" of the condition, according to Watson-Jones, is greater limitation of active than of passive abduction in the presence of a normally contracting deltoid. Weak abduction to about 60° is possible but no more; there is no true glenohumeral abduction. Conservative treatment involves immobilization of the shoulder with the arm at 90° abduction and 60° external rotation for 8 to 10 weeks by the use of a frame and meanwhile active exercise for fingers, wrists and elbows.<sup>1006</sup> According to some the opening between the subacromial bursa and the shoulder joint will never heal and must be repaired surgically. The technic was described.<sup>279</sup> Of 12 patients so treated four had excellent results, four good, three fair and one poor (Outland and Shepherd).

Partial or complete rupture of a supraspinatus tendon may cause secondary effects in adjacent tissues: chronic subacromial bursitis, eburnation and rounding off of the greater tuberosity, degeneration, fraying and eventual rupture of the long head of the biceps, excrescences and osteophytes along the edge of the acromion and the tip



of the greater tuberosity, slight erosion of articular cartilages of the shoulder joint (Ferguson).

4. *Subacromial (Subdeltoid) Bursitis (with and without Calcification)*. Four types of bursitis were again listed by Ferguson (features of which were noted in our last Review): acute traumatic bursitis without calcification, acute bursitis with calcification, chronic bursitis with or without calcification and chronic adhesive or obliterative bursitis. The last was characterized by atrophy of shoulder muscles and very limited motion of joint and was called the "frozen shoulder" (a term which others reserved for a condition to be described hereafter). Cases of simple subacromial bursitis are rare<sup>1000</sup>; usually bursitis and tendinitis with or without deposits of calcium *beneath* the bursa are present. Occasionally infection but usually trauma was considered the cause.<sup>208</sup> Symptoms are about the same as those of tendinitis. In Collins' experience the pain was usually greater at night and was most severe at the insertion of the deltoid and "seldom over the region of the bursa." Among Rubert's 288 cases of "subdeltoid bursitis" there were pain and limited motion in 95 per cent, a tender point over the greater tuberosity in 58 per cent, muscle atrophy in 20 per cent, atrophy of the head of the humerus in 22 per cent, associated arthritis in 16 per cent, calcification in the region of the bursa in 18 per cent. In 15 per cent pain extended to the deltoid insertion and sometimes to the neck and down the arm to the wrist.

In acute cases rest, heat and morphine are required. Injection of 15 to 20 c.c. of 1 or 2 per cent solution of procaine into the bursa and the capsule of the shoulder joint was recommended.<sup>208, 471</sup> In 18 cases the average disability after such treatment was 4.7 days.<sup>471</sup> Injections of 500 c.c. or more of "normal saline" solution were used by some<sup>208</sup> to distend and rupture the painful sac. Spontaneous recovery often occurs. If conservative therapy fails, the bursa should be explored and the deposits of calcium and thickened fringes removed (technic given).<sup>208</sup> In 147 of Rubert's 168 cases conservative treatment was used; results were good in 69 per cent, moderate in 19 per cent, poor in 12 per cent; in those cases in which surgical treatment was employed results were good in 48 per cent, moderate in 24 per cent, poor in 28 per cent.

5. *"Periarthritis of the Shoulder": "Scapulohumeral Periarthritis."* This was described by Duplay in 1872, but the term "periarthritis humeroscapularis" is considered poor by some.<sup>81</sup> Other names are Duplay's syndrome, and scapulohumeral fibrositis. The condition results from trauma or from "rheumatic fibrositis."<sup>1006</sup> It may be closely related to the syndromes already described in this section: in one of Duplay's cases which came to necropsy the inflammation apparently had spread from a subacromial bursa to neighboring structures. Among Douthwaite's 37 cases the main causative factor was trauma in 12, fibrositis in 14, unknown in 10; in one case the condition came on after hemiplegia. The condition was on the right in 21, left in 15, bilateral once. Symptoms arise spontaneously or after trivial trauma. The joint is not swollen. Pain is *not* confined to the greater tuberosity or region of the supraspinatus but is diffused and there are many tender spots. Internal rotation and forward and backward flexion may be free but abduction and external rotation are limited first by muscle spasms, then by adhesions about the whole joint capsule, "the frozen shoulder." Roentgenograms generally do not indicate any abnormality.<sup>252, 1006</sup> For the acute stage rest with the arm in abduction, heat, massage and hydrotherapy especially were recommended<sup>211</sup>; injections of procaine hydrochloride were less helpful than in other conditions.<sup>471</sup> "Most important" is active exercise ten minutes every hour of the day and the "worst treatment" is manipulation of the shoulder under anesthesia. The latter increases the serofibrinous exudate (Watson-Jones). Others,<sup>302</sup> however, favored such manipulation; results were excellent in 95 per cent of Douthwaite's cases. Dilaudid was used for severe "post-manipulation pain."

6. *Fractures and Other Traumatic Lesions of the Shoulder.* Fractures and dis-

locations of the shoulder may be associated, of course, with some of the aforementioned syndromes.<sup>883,1006</sup>

7. *Tenosynovitis of the Long Head of the Biceps Brachii*. According to Schrager this is a "new" entity described by F. Pasteur, 1932, unknown to American literature, but the commonest cause of shoulder pain. It may be caused by trauma or infection. In acute cases pain and disability are severe. Schrager tabulated the features distinguishing it from the other conditions just described. The most important diagnostic feature is tenderness and pain in the bicipital groove. The patient cannot raise the arm above the level of the shoulder (not even with assistance), nor can he abduct it or place the dorsum of the hand against the back. In acute cases treatment consists of morphine, rest in bed, support of the arm by pillows, and diathermy. Much benefit and occasionally "instant cures" can be obtained by sudden traction (rationale and technic given). In less acute cases diathermy, massage and exercises were used.

8. *Calcification of the Bursa of the Coracoclavicular Ligament*. This represents another possible cause for painful shoulders. In McCurrah's case, presumably the first one reported, pain and swelling below the outer part of a clavicle appeared some months after a fall on the shoulder. A large calcified deposit was found in the region of the coracoid process and excised. Its position was much more mesial than that of deposits previously mentioned.

9. *Pulmonary Tumor Simulating Subacromial Bursitis*. Symptoms characteristic of subacromial bursitis developed in one case. "Calcified subacromial bursa" was removed but symptoms persisted and later were found to be due to a slowly growing neoplasm of the apex of the lung, a superior pulmonary sulcus tumor (Nathanson, Hochberg and Perlman).

10. *Shoulder Pain from Cervical Ribs*. Stinchfield reminded us that symptoms resembling "arthritis" of the shoulder occasionally may result from such developmental anomalies as cervical ribs.

## DISEASES OF MUSCLES AND FIBROUS TISSUE

*Classification*. Bach divided diseases of muscles as follows: (1) diseases of muscles secondary to diseases of bones and joints, (2) primary diseases of muscles caused by (a) infective or toxic agents, (b) metabolic changes, (c) trauma, (d) mechanical or static agencies. His classification of "muscular rheumatism" follows:

- I. Those essentially inflammatory and infective in origin.
  - A. Diffuse septic myositis (i.e., metastatic abscesses).
  - B. Dermatomyositis.
  - C. Myositis ossificans.
  - D. Myositis fibrosa.
  - E. Myositis secondary to "focal infection."
  - F. Muscle lesions of glanders.
  - G. Muscle lesions of echinococcal infections.
  - H. Muscle lesions of gonorrhea.
  - I. Muscle lesions of syphilis.
  - J. Muscle lesions of tuberculosis.
  - K. Muscle lesions of typhoid fever ("Zenker's degeneration").
  - L. Muscle lesions of scurvy (intramuscular hemorrhages, localized inflammation).
  - M. Muscle lesions of hemophilia (hemorrhages, localized fibrosis).
  - N. Muscle lesions of rheumatic fever.
  - O. Muscle lesions of subacute bacterial endocarditis.

## II. Those which are noninflammatory and usually not infective.

## A. Myalgia associated with other conditions.

1. Extraneous physical causes, e.g., chilling ("fibrositis," "myogeloses").
2. Fatigue, overexertion, acute trauma.
3. Metabolic disturbances such as gout and high blood pressure.
4. Drug therapy ("les rhumatismes de la chimiothérapie"), e.g., arsenic, bismuth, mercury, gold, barbiturates, chloral, antipyrin, atophan.
5. Chronic nervous exhaustion, inferiority complex, etc. (psychoneurotic rheumatism).

## B. Panniculitis.

Bach's descriptions of these types were too brief to be helpful in diagnosis. Bach and also Gutstein noted that obese women with high blood pressure often have vague rheumatic pains ("hochblutdruck-rheumatismus") in neck and shoulders, extending down the arms, sometimes also to the thighs. Concerning myalgia from chemotherapy Bach stated: "The clinical signs vary from transient muscle pain to hydrarthroses." Bach accepted Gower's view that despite specific differences the various forms of "chronic myositis" have a basic identical pathologic picture: an inflammatory reaction in connective tissues.

[This classification has certain inconsistencies, but is here given because of the rarity of such classifications.—Ed.]

## DISEASES OF MUSCLES CAUSED BY TRAUMA

A general discussion of the types and treatment of muscle injuries was given by Page.

*Rupture of Biceps Brachii.* Waugh stated that rupture of the biceps brachii occurs more frequently than is generally believed. He noted 14 cases among 28,755 cases admitted to two general hospitals. Causes of the conditions were indirect trauma in seven, direct trauma in four, stabbing in one, unknown in two cases. The long head and its tendon were affected in 12, the "lower" tendon in two cases. Including the latter, 25 cases of ruptured "lower" tendons have been reported in the literature. Symptoms and signs were discussed. The most constant sign was a deforming change in the contour of the muscle. Treatment should be conservative in cases of partial rupture or little disability. Surgical repair is indicated in others; it was done in 12 of the 14 cases.

*Myositis Ossificans.* Geschickter and Maseritz studied 25 cases of myositis ossificans, 23 of the circumscribed, 2 of the progressive type. The usual cause was trauma (in 60 per cent of the cases); sometimes the cause was unknown. Occupation played no rôle. The thigh was affected in 13 cases, the arm in five, elbow in two, lumbar region and neck in one each, multiple regions in one, and unstated regions in two. Pathologic reactions were described. Conservative treatment was recommended (no details given) since postoperative recurrences were common. In the four other cases reported involvement occurred in the biceps after injury to the elbow,

the anterior axillary fold after fracture of the humerus,<sup>674</sup> a tendo achilles after injury (16 such cases in the literature)<sup>354</sup> and in tissues in a suprapubic scar near the left pubic bone, involved after prostatectomy.<sup>846</sup> Only eight cases of postoperative myositis ossificans have been reported. Page noted that the disease may occur after the excessively tight application of a tourniquet. He advised complete rest of the affected part in a plaster cast for several weeks. Resorption of ectopic bone may occur. Surgical excision should be performed only in cases more than one year old that have limitation of motion in an adjacent joint.

### INFECTIOUS MYOSITIS

Three cases of nontuberculous iliopsoas abscess were reported, two from *Staphylococcus aureus* (Lewis), one from gram-positive diplococci in a case of pneumonia. In the latter bilateral psoas abscesses, the first on record (Ortmayer), were present.

### FIBROSITIS

Most articles on fibrositis concern that type of unknown etiology which some call "primary fibrositis." When fibrositis appears as a recognized part of some definite general disease (e.g., rheumatic fever) it is (or should be) spoken of as "secondary fibrositis."

*Primary Fibrositis.* Clinical features. The disease is common among London busmen.<sup>915</sup> Its clinical features and the characteristic painful, aching stiffness it produces were again described.<sup>377, 397, 525, 750</sup> Comments were made on two anatomic types of fibrositis less well-known than others: spinal fibrositis and fibrositis of the abdominal wall. Patterson considered the latter more common than supposed (no details given). Gordon considered spinal fibrositis (acute and chronic lumbago) "the most important rheumatic affection of the spine." The frequent presence of tender spots with thickened bands, plaques and nodules was noted. Some of the indurations are tender, others are not. "Hence, while the presence of a thickening is a necessary prelude to an attack of fibrositis, acute or chronic, the thickening must, so to speak, be awakened into activity before the attack is precipitated."

The ameliorating effect of various types of jaundice in nine cases and of pregnancy in two cases of primary fibrositis was noted by Hench; its possible significance has already been discussed herein.

Laboratory data. Arneth counts were essentially normal.<sup>357</sup>

Pathology. No new data were offered. Writers continued to quote Stockman (1920) thereon. The fibrotic thickenings were interpreted as local tissue reactions to irritating deposits of some sort.<sup>377</sup>

Etiology and pathogenesis. The usual etiologic factors were mentioned: trauma, exposure to cold, "metabolic changes," influenza, tonsillitis and other infections.<sup>135, 612, 750, 954</sup> These are probably only predisposing and precipitating factors: the real cause is unknown. The assumption that the ir-

ritating material is necessarily of bacterial origin "has been all too hastily and uncritically accepted"; it is probably sometimes of bacterial, at other times of metabolic origin, perhaps related to accumulated muscle metabolites (Gordon). The similarity of fibrositic symptoms to the aching stiffness from muscle exertion is too close to be overlooked; the rôle of lactic acid and other muscle metabolites in this disease deserves reinvestigation (Patterson). Freund considered unproved the idea that fibrous tissues are predominantly affected in nonarticular rheumatism. "Fibrositis is certainly a misnomer and should be replaced by the term non-articular rheumatism, or even better, muscular rheumatism, if it could be proved that any rheumatic pain and stiffness are caused by pathological changes in certain muscles or tendons. . . . Whatever the primary cause and the contributing factors may be [the myalgic spot] is brought about by a temporary spasm in the capillaries leading after some time to a hardening of the muscles which might be described as congelation." Some writers suggested that the disease is related to an "imbalance of electrolytes," a disturbance in the calcium-potassium-sodium ratio of muscles.<sup>335, 397, 750</sup>

Treatment. Removal of infected foci was advised generally, but its results were often disappointing.<sup>377, 531</sup> Strapping and extra rest were used for acute localized fibrositis. Each form of physical therapy had its adherents: infra-red,<sup>63, 64, 397</sup> hot packs and douches,<sup>377, 953, 954</sup> brine baths<sup>696</sup>; ultraviolet irradiation seemed useful to some,<sup>63</sup> of little value to others.<sup>377</sup> "The sheet anchor of treatment is the right sort of massage together with sweating. Just any massage will not do" (Gordon). Muscles must be relaxed and the nodules must be kneaded against subjacent bone, sometimes a "very painful business." The skin should be "improved by a hardening process" (undescribed).<sup>42</sup> Intramuscular injections of oxygen or of procaine hydrochloride were recommended.<sup>42</sup> In his cases Kellgren noted wide areas of "referred pain and tenderness" associated with much smaller tender spots. The latter were considered the chief sites of disease since pressure thereon reproduced the patient's more diffuse complaints. Into these spots 5 to 70 c.c. of 1 per cent procaine were injected in eight cases of fibrositis of 2 to 52 weeks' duration. After a momentary exacerbation of the referred pain symptoms promptly disappeared. [The follow-up periods were usually only 1, never over 3 weeks.—Ed.] Excellent results presumably followed injections of sterile milk<sup>612</sup> or histamine.<sup>254</sup> Douthwaite<sup>253</sup> considered the use of iodine beneficial, gold salts "probably inadvisable." Injections of bee venom were considered useless by some,<sup>254</sup> useful by others<sup>144</sup>; Reichart injected it into the tender nodules and reported notable relief after 1 to 10 injections in some cases. The diet commonly used was to control obesity and constipation.<sup>135, 377</sup> Gutstein prescribed a salt-free, vegetarian diet to eliminate the sodium and increase the intake of potassium and calcium. By the use of this diet and other measures he "cured" 48 of 52 patients. Manipulation under anesthesia was recommended in cases of fibrositis of spine or shoulders with considerable stiffness.<sup>377, 759</sup>

Secondary fibrositis. Comments on the involvement of fibrous tissue in gonorrhea, in atrophic arthritis and in hypertrophic arthritis ("senescent fibrositis") have already been made herein. Several writers discussed "gouty fibrositis." <sup>136, 359, 449, 956</sup>

### MISCELLANEOUS DISEASES OF MUSCLES

*Psychoneurotic Rheumatism or Myalgia.* Halliday extended his thesis (outlined in our last Review) that fibrositis is a definite entity but that many cases of so-called fibrositis really represent "psychoneurotic rheumatism."

If for any reason an emotional reaction is maintained for some time, illness may result. The emotional reaction may "emerge" into any one of several symptom-complexes including one somewhat resembling "fibrositis" or "rheumatism." Methods for carrying out the proper psychologic examination were described. Especially prone to psychoneurotic rheumatism are persons aged 35 to 45 years, widows and widowers, married persons who live apart, lonesome persons, miners, workers at heights (steel workers), clergymen, typists, housekeepers, nurses, pieceworkers, teachers, traveling salesmen, and "those in sheltered clerical occupations in which the instinct of creation is continuously thwarted." The condition commonly affects parts of the body previously injured or operated on. The complaints are often expressions of "symbolism." It is especially difficult to diagnose the condition and treat those persons in whom true fibrositis antedated or followed the onset of psychoneurotic rheumatism. Gutstein agreed that psychoneurotic rheumatism exists but considered it less common than suggested by Halliday.

*Epidemic Myalgia or Pleurodynia.* MacDonald again reviewed the studies made by himself and others on 70 children affected in a recent Cincinnati epidemic: these were noted in our last Review.

*Dermatomyositis.* An interesting case was seen by Lane: a young woman had an erythematous edematous rash three days after alveolectomy. Pains of joints and muscles and leukopenia developed. A diagnosis of lupus erythematosus disseminatus was entertained until muscle tenderness and edema developed. The diagnosis of dermatomyositis was confirmed by biopsy of muscle. A preëxisting carcinoma of breast was present. Post-mortem findings were reported. The similarity of dermatomyositis and lupus erythematosus disseminatus was stressed, common symptoms being rash, edema, fever and pains of the joints. In the former leukopenia is rarely present and pain is more muscular; pain in joints and leukopenia characterize the latter.

*"Muscular Rheumatism Associated with Spina Bifida Occulta."* Ditrich attempted to show that "muscular rheumatism" even in the upper extremities is "invariably" caused by disturbances of sacral nerve roots associated with spina bifida occulta and that surgical correction of the spinal condition eliminates the muscular symptoms. Ten cases were described: their muscular pains and tenderness were mostly in the feet (usually with pes equinus) but also in thighs and low in back, occasionally in upper extremities. Tendon reflexes of knees and ankles were usually abnormal; constipation and colonic spasm were present. At operation the first, second and third

sacral laminae were removed, also deposits of "fibro-adipose tissue" overlying the dural sac and nerve roots. Thereafter muscle tenderness, pain and spasm were eliminated "in all cases." The mechanism of relief was admittedly not clear. Elimination of symptoms in muscles supplied by sacral nerves "would indicate a direct nerve effect" but the relief in other muscles and the improved intestinal tone suggested a systemic effect: perhaps an intestinal toxemia of etiologic importance was corrected.

[The writer's clinical description of "muscular rheumatism" is vague. His emphasis on the presence of pains of the feet and aching fatigue in muscles of legs and feet with deformities of the feet suggests that postural muscle fatigue was present and not true muscular rheumatism or "fibrositis." It is difficult to relate these symptoms to spina bifida occulta.—Ed.]

### MISCELLANEOUS CONDITIONS

*Aseptic Necrosis of Bone.* Among 10 patients with aseptic necrosis of bone from arterial occlusion studied by Hirsch were four with chronic pain in joints adjacent to the affected bone; symptoms resembled "arthritis." The causes of the vascular constrictions or occlusions were not clear; trauma had occurred in seven cases. Inflammatory reaction and occlusion by fibroblastic tissue of affected vessels resulted in localized infarction of bone. Secondary articular changes were sometimes produced. If large enough, infarction of bone is evident in roentgenograms.

[Perhaps some such process is related to certain types of hypertrophic arthritis in hips with cystic regions in bone. Unfortunately no roentgenograms of joints in these cases were published.—Ed.]

*Periarteritis Nodosa.* Although still uncommon, this disease is not as rare as was once thought. Since first described by Kussmaul and Maier (1866) at least 395 cases have been reported; a clinical summary of them is being made (Boyd). It is a vascular disease of unknown origin. The lesions are so widely distributed throughout the body that a protean and often bizarre clinical picture is produced; hence until recently it usually has not been diagnosed before death. The clinical features are those of infection, and include irregular fever, sterile blood cultures, weakness, prostration in acute cases, cachexia, secondary anemia, leukocytosis, eosinophilia (up to 79 per cent of leukocytes) in 12 per cent of cases, in addition to the signs and symptoms from the vascular lesions in the various affected organs (heart, kidneys, lungs, appendix, gall-bladder, skin, etc.). It is often mistaken for "rheumatism" because of symptoms referable to nerves, muscles and joints. A true neuritis often occurs. The focal myositis produces muscle pain and tenderness which sometimes are worse at night. The fever and diffuse pain in muscles and joints may resemble "rheumatic fever." Eleven new cases were reported. In some of them symptoms included severe cramps in the legs, called "rheumatism" (Sandler), pain in extremities (Ashour; Berger and Weitz), pain in muscles and joints of extremities and true neuritis (Kernohan and Woltman). Vining's case was of special

interest. Initial symptoms included generalized pain, fever, muscle soreness and a red swollen wrist. The initial diagnosis was rheumatic fever. From time to time there was swelling of joints, presumably from periarticular nodular erythematous formations rather than from synovitis. Later arms were flexed and a shoulder was fixed and painful. A connection between periarteritis nodosa and rheumatic fever has been suggested.<sup>190, 990</sup> Among 100 unselected cases of the disease reviewed by Boyd were 34 with a history of rheumatic fever.

[One of us, M. H. D., recently saw a patient with marked articular changes and subcutaneous nodules resembling those of atrophic arthritis. Diagnosis of periarteritis nodosa was proved by autopsy. He also has seen two other patients with atrophic arthritis who later had periarteritis nodosum proved at autopsy.—Ed.]

*Disseminated Lupus Erythematosus.* Chief features of this disease are fever, articular symptoms, leukopenia and eruption on skin, later nephritis. The eruption on the skin often antedates the articular pain or the two may appear together. Occasionally the fever and pain antedate the eruptions; such cases resemble rheumatic fever somewhat.

A case was reported<sup>165</sup> in which symptoms included fatigue, loss of weight, cough, fever, sore muscles, attacks of hot swollen joints, persistent cutaneous lesions and hemorrhagic tendency. Splenectomy was done for "thrombocytopenic purpura." Severe recurrent polyarthritis, not just arthralgia, occurred; the leukocyte count was 4,000. Subsequently a diagnosis of lupus erythematosus disseminatus was made and proved at necropsy but in addition typical vascular lesions of periarteritis nodosa were present.

*Arachnodactylia (Marfan's Syndrome, 1896).* Features of this disease are abnormally long fingers and toes, decreased subcutaneous fat, generalized underdevelopment of muscles, ligamentous relaxation, sometimes bilateral dislocation of the lens with tremulous iris, deformities of joints, especially of feet with contractures, and certain other developmental defects. About 200 cases have been reported. Two more are described (Futcher and Southworth).

*Calcification of Hyaline Cartilage.* Cartilage from ribs, bronchi, trachea and larynx was obtained at autopsy from 97 men and 105 women. Falconer concluded that calcification of hyaline cartilage is common after 50 years of age. Cartilages of ribs of men are most often affected, those of trachea and bronchi of women.

#### OTHER STUDIES ON JOINTS AND RELATED TISSUES

*Articular Physiology.* By a modification of methods used to isolate chondroitin-sulfuric acid from cartilage Meyer, Smyth and Dawson obtained from synovial fluid a sulfur-free and phosphorus-free polysaccharide apparently identical with hyaluronic acid, the polysaccharide isolated from bovine vitreous humor, human umbilical cord and hemolytic streptococci (Lancefield, Group A). Its presence in the latter seems significant in view



of the possible relationship of those bacteria to joint diseases. Iob and Swanson reported studies on extracellular and intracellular water in bone and cartilage. The proportionate distribution of mucin in 168 specimens of human synovial tissue from inflamed joints, tendovaginal coats and bursae, stained by Mayer's mucicarmine method, was studied by Cherry and Ghormley. It was concluded that synovial mucin results from cellular disintegration and not from a true secretion.

[One of us, W. B., does not agree.—Ed.]

A theory that an alternating ischemia and hyperemia, produced by the contraction and relaxation of muscles, maintains normal calcification of bone was presented by Blair. Hyperemia causes rarefaction, decalcification of bone and osteoporosis; a relative ischemia produces consolidation of bone (Grieg, 1931; Jones and Roberts, 1934). Maintain the circulation within certain limits and bones remain unchanged. If hyperemia produces resorption of bone, the use of heat in certain conditions (e.g., recent fractures) is wrong, according to Blair. Heat should be used only when it is desired to absorb calcium, as for example, in calcification of subdeltoid bursa or other heterogenous calcification [e.g., myositis ossificans. Some of us have found heat useless in myositis ossificans.—Ed.] "The use of heat in acute bone atrophy is a vicious practice, because it increases the pain and absorption of bone. Massage should also be used with discretion in the presence of atrophic bone as it too increases circulation. The value of contrast baths may be due to the fact that it produces an alteration of the blood supply to the part." In cases of bone atrophy of a part, as in fracture [or atrophic arthritis?—Ed.] Blair advised, on theoretical grounds only, the use of alternating suction and pressure to increase and diminish the blood supply.

[This paper is hypothetical but also thought provoking.—Ed.]

Additional papers of interest were those on the relation of cartilage to the repair of bone,<sup>91</sup> the effect of hypertrophic cartilage on growth of bone marrow,<sup>475</sup> the evolution of the knee joint,<sup>440</sup> and the morphogenesis of the architecture of the shoulder, hip and thigh.<sup>472, 473</sup>

*Articular Roentgenography.* Improvements in roentgenographic technic were reported. All roentgenograms of shoulders should be made with the patient upright, not lying down, for details of the joint are then more clear.<sup>186</sup> With Ottonello's method the second cervical vertebra and those below it can be shown on one film.<sup>487</sup> A technic was devised to obtain better true lateral projections of the thoracic portion of the spine.<sup>318</sup> By taking anteroposterior views of clavicles with the patient *standing* 72 inches from the tube both acromioclavicular joints can be visualized without distortion in one roentgenogram.<sup>462</sup> The little known technic of Gaenslen (1936) was considered best in obtaining lateral views of hips.<sup>189</sup>

Pneumoroentgenography of knees was considered simple, harmless and valuable in the diagnosis of internal derangements, osteochondritis dissecans, chronic villous synovitis, hypertrophied fat pads, Baker's cysts and loose bodies. Correct diagnoses as verified by arthrotomy, were made in 87 per

cent of one series,<sup>784</sup> in 97 per cent of another.<sup>411</sup> Injections of sterilized oil into joints for diagnostic purposes was considered useless, sometimes harmful.<sup>495</sup>

*Articular Function.* A small compact pendulum arthrometer useful for measuring improvement in joint motion was described.<sup>413</sup>

*Experimental Arthritis.* 1. Infectious. Certain hemolytic and green-producing streptococci, given intravenously to rabbits by Cecil and Angevine in single, much smaller doses than generally used, produced in many rabbits a *nonsuppurative* proliferative polyarthritis similar to, but admittedly not completely identical with, human atrophic arthritis. Streptococci disappeared from the blood stream within a few days after the injection and did not reappear. They were grown repeatedly from aspirated synovial fluid during the first week but rarely after three weeks even though articular changes persisted as long as 18 months.

[The large doses of bacteria previously used by most workers generally produced acute suppurative lesions and not *chronic* nonsuppurative polyarthritis. In this study one of the nearest approaches to the experimental production of a bacterial arthritis simulating human atrophic arthritis was made.—Ed.]

2. Chemical and nutritional. Extracts and implants of the anterior lobe of the pituitary given to guinea-pigs not only altered endochondral ossification but also produced degenerative and hypertrophic changes within the joints, chiefly swelling of the chondromucoid matrix, atrophy and degeneration of whole rows of cells in epiphyseal cartilage, hyperplasia and hypertrophy of cells in different layers of the epiphyseal cartilage, chondrophyte and cartilaginous covering of the joint (Silberberg and Silberberg).

[In the light of these results it is interesting to speculate as to whether the anterior lobe of the pituitary plays any rôle in the production of degenerative changes in human cartilage which antedate primary hypertrophic arthritis.—Ed.]

The Silberbergs also noted the effect of thyroid extract and of potassium iodide on the bone and cartilage of immature guinea-pigs. Thyroid hormone caused slight hyperplasia, marked hypertrophy and an accelerated differentiation of euhyaline cartilage of epiphyseal line, ribs, joints and vertebrae. Potassium iodide had a stimulating effect on the proliferation and differentiation of euhyaline cartilage, but also produced retrogressive processes in cells and intercartilaginous matrix, slight absorption of bone, and destructive changes in joints caused by chondroclastic activity.

The lesions of cartilage and bone resulting from experimental scurvy in guinea-pigs were described (Ham and Elliott).

*Physiology of Muscles.* Despite the fact that the chronically stiff, aching muscles of hundreds of thousands of Americans daily make their lives uncomfortable and unhappy, we know little or nothing about the altered physiology of diseased muscles even in such common states as muscular rheumatism or "fibrositis." Compared to joint tissues human muscle is much more available for biopsy and study, but most physicians would not know how to examine chemically a piece of diseased or painful muscle after

removal. Data on the physiologic reactions of normal muscle are rather extensive but only a pitifully small amount has been applied to the treatment or understanding of muscle diseases. Would not the coördinated efforts of a rheumatologist, a clinical pathologist and a physiologist or student of muscle chemistry be most fruitful if directed to a clinico-chemical study of diseased muscles? There must be many chemical discoveries of great significance, just waiting for the application to diseased muscles of analytical methods already available and already used on normal muscle. Their application might do much to elucidate the cause, for example, of muscle weakness in atrophic arthritis, of muscle stiffness and pain in fibrositis or muscular rheumatism and of the "eternal tiredness" present in both these diseases. To such a group of investigators a number of current<sup>58, 170, 272, 381, 580, 620, 633, 704, 869, 895, 903</sup> reports should be of interest, especially those on the chemistry of muscle contraction,<sup>823</sup> the effect of exercise on blood, lymph and muscle in relation to muscle soreness,<sup>100</sup> the chemical composition of voluntary muscle in muscle disease (including one case of "diffuse myositis"),<sup>799</sup> observations on referred pain arising from muscle,<sup>526</sup> differences in temperature of skin and muscles of lower extremities following various procedures,<sup>337</sup> and on the estimation of fiber, fat cells and connective tissue in muscle.<sup>45</sup>

*"Comparative Rheumatology": Rheumatic Diseases in Animals.* Horses suffer rather uncommonly with spondylitis ankylopoietica, but commonly with spondylitis osteo-arthritis "as met with in man," according to Mitchell whose necropsy studies on horses with osteo-arthritis suggested that the disease called "shivering" (tremors in voluntary muscles, difficulty in using hind legs) may be due to the pressure of exostoses on nerve roots going to the lumbosacral plexus where they emerge from the intervertebral foramina. Fusion of osteophytes and ankylosis in the lumbar region frequently occur in hypertrophic spondylitis in animals (in contrast to its rarity in humans so affected). Degeneration of intervertebral disks occurs in old horses.

#### THE CAMPAIGN AGAINST RHEUMATISM

During the year under review the progress made in the campaign against rheumatism was considerable even though unspectacular. The world-wide extent of the scourge and its huge cost in terms of economic loss and human suffering were made only too clear at the International Congresses on Rheumatic Diseases held at Oxford and Bath which were attended by about 375 delegates from 23 countries. A summary of what is being done to further the campaign in the various European countries was made by Fox. In some countries medical research on rheumatic diseases has increased greatly. Other countries are devoting themselves mainly to new efforts along the lines of prevention and cure; still others are chiefly occupied in educational work and propaganda to improve the occupational and social conditions of rheumatic persons.

England was accused recently of having "the greatest culture with regard

to the study of rheumatic diseases and the worst organization, for the attainment of practical success." <sup>241</sup> But British physicians are doing their best to refute the charge. Since 1929, when the first step was taken in the establishment of the Red Cross Clinic for Rheumatism in London, much has been done, culminating in the formation (1936) of the Empire Rheumatism Council. This council has the earnest support of the Ministry of Health <sup>365</sup>; already its influence is being felt and its work extended to the dominions and colonies. <sup>267, 314, 728</sup> The objectives of the Empire Rheumatism Council were described again in detail. <sup>467, 1033</sup>

Requisites necessary for the success of any campaign against rheumatism include (1) the establishment of an intelligence department to obtain adequate information on all phases of the problem, (2) a definite policy and plan of action, (3) action (Fox). Since "few campaigns can afford to wait until intelligence is complete" tentative, even experimental, advances are fully justified.

According to Davidson and Duthie the problem of rheumatism has not and will not be solved by the spas and voluntary hospitals as they are now run. Voluntary hospitals do not have sufficient beds or physiotherapeutic facilities for the proper management of the great army of rheumatics. Many physicians in the voluntary (i.e., privately endowed) hospitals have little interest in, indeed some have an active distaste for, cases of rheumatism, a distaste born of their ignorance of the disease and what can be done for it. Few physicians in these hospitals have had the special postgraduate training required for the diagnosis and treatment of the rheumatic diseases. "Rheumatology is the most difficult of the medical specialties because of the complexity of the etiology and the diversity of the forms of treatment required." Spas have distinct advantages but are relatively inaccessible for most patients who will not go to spas in the early stages of their disease. The spa hospitals have insufficient beds. The climate at the spas is often suitable only "in-season." Physicians at spas have great difficulty in obtaining adequate follow-up records on the end results of treatment. For these reasons Davidson joined with other British physicians <sup>157, 207, 212, 320, 365, 787</sup> in recommending the following as important for the complete success of the campaign in their country.

The recommendations are: (1) the establishment of a central bureau for the collection and distribution of statistics; (2) a study of those public health problems related to the development and prevention of the rheumatic diseases (e.g., poor housing, inadequate food and warmth, etc.); (3) the adoption by public health authorities of legal weapons to cope with these predisposing and precipitating factors; (4) prevention of dietary deficiencies among school children, e.g. by increasing their consumption of milk, (5) training of children in proper posture; (6) extension of the dental service of the National Health Insurance Scheme to increase the dental care of juveniles; (7) prevention of undue fatigue among children and workers; (8) social welfare work among industrial workers to minimize mental as well as physical strain; (9) establishment of rheumatism departments (units) for the care of in-patients in every general hospital, and the enlargement of those now in existence; (10) establishment of rheumatism clinics or centers for the care of out-patients in all cities; these

should preferably be part of a general hospital; (11) establishment of consultation centers connected with large hospitals in various cities; (12) development of research units in these various departments and clinics, groups of clinicians coöperating with a pathologist, bacteriologist, biochemist and physiologist to study the cause of the disease and to determine the comparative value of the manifold rheumatism treatments (the problem is that *too many* people seem to be able to "cure" rheumatism); (13) establishment of one or more postgraduate schools of rheumatology; (14) training of more physicians in this specialty, to be put in charge of the various units and centers and to devote their full time to the prevention and treatment of rheumatic diseases; (the specialist in charge should, wherever possible, hold a university position; although a specialist, he should enlist in the patient's behalf the coördinated effort of all branches of medicine); (15) a uniform plan of history taking; (16) a uniform scheme for estimating results of treatment; (17) increased provisions for physical therapy in cities and towns not possessing a spa; (18) a change in the National Health Insurance to allow panel fees and payments for physical therapy as well as for medicines; (19) an adequate scheme for the supervision by physicians, visiting nurses and social workers, of after care and its maintenance for at least 6 to 24 months after a patient is discharged from a hospital, spa or "center"; (20) a study of comparative rheumatology: how articular diseases affect animals.

Since it is financially impossible for voluntary hospitals to provide sufficient accommodations or means to carry out these activities, the problem must be handled by municipal and national authorities.<sup>240, 241, 307, 787</sup> The scheme should be under government supervision and given governmental financial support as necessary. "The acceptance of the control of rheumatism as a public health function is the most important measure in solving the problem."<sup>241</sup> But public health authorities cannot institute such a scheme without the support of public opinion. Hence according to Davidson, the most urgent problem in connection with chronic rheumatic diseases is political, not medical: the education of the people as to the extent of the scourge so that they will provide the necessary facilities for its elimination. Propaganda with "the right tone" is a most valuable and powerful weapon and physicians should use it unashamedly to further this end (Fenton; Horder). The public must be told about the insidious and serious nature of rheumatism, and that each individual can do certain things to prevent or ameliorate it; the public should know where proper facilities for treatment are and be encouraged to use them. But in using such propaganda an inviolable principle must be "truth in advertisements" lest false hopes be raised. To maintain the dignity of the medical profession all sensationalism must be avoided.<sup>299</sup>

Chief sponsors of the campaign in the United States are the American Committee for the Control of Rheumatism and the American Rheumatism Association. The organization and purposes of this association and the extent of the problems it faces were outlined in bulletins<sup>25</sup> sent to lay members and others. These are intended to supplement the articles on rheumatic diseases published for laymen in "Hygeia."<sup>229</sup> Of the international campaign Sir William Willcox recently wrote, "The movement has past the dangers of infancy and now enters on the stage of vigorous youth." It is sincerely hoped that this "vigorous youth" will not, like so many others,

be lost through the war. It is tragic indeed that the fine coopération expressed through the activities of the Ligue Internationale Contre le Rhéumatisme must be temporarily suspended, but it is confidently expected that the campaign, though perhaps retarded by the war, will be renewed with increased vigor afterward, so that the hope of its sponsors may be realized; that perhaps within a decade the rheumatic diseases can be largely brought under control.

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Because their contents were not indexed in the Quarterly Cumulative Index Medicus we inadvertently omitted the contents of two new journals devoted to rheumatic diseases: *The Harrogate Spa Medical Journal* (Harrogate) and *Rheumatism* (London). Their contents will be reviewed in the next Review.

The chairman of the editorial committee for this review will welcome the receipt of reprints from authors of current (1939-1940) articles which will greatly facilitate the preparation of subsequent reviews.

# CASE REPORTS

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## DISSECTING ANEURYSM OF THE AORTA WITH A CASE REPORT\*

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It is a strange fact that dissecting aneurysm of the aorta, which presents such dramatic symptoms and about which so much has been written, is so rarely diagnosed during life. About 500 cases have been reported in the literature of which only 12 were diagnosed ante mortem. The condition usually occurs in patients between the ages of 40 and 70 years suffering from hypertension and arteriosclerosis. Syphilis, which is a questionable etiologic factor, appears to be present in only 10 per cent of the cases. The normal aorta can withstand great internal pressures, from 900 to 1500 millimeters of mercury. Nevertheless, instances of rupture following a sudden rise in pressure have been reported in young individuals in whom no disease of the aorta could be demonstrated. Shennan<sup>1</sup> reports three cases in males aged 13, 23, and 32 years respectively in which the lesion was apparently produced by unusual athletic exertion. In a number of cases trauma appeared to be the direct cause of the aneurysm.

According to McGeachy and Paullin<sup>2</sup> sclerosis of the vasa vasorum causes degenerative changes in the media thereby weakening its structure. Tyson<sup>3</sup> stated that obliterative changes in the vasa vasorum from atherosclerosis or other types of low grade inflammation lead to medial degeneration. He concluded that the aneurysm begins by the rupture of one or more of the vasa vasorum into the weakened media, and that a tear in the intima is not essential to the formation of the dissecting aneurysm, but occurs secondary to its development. On the contrary, Shennan believes that "deleterious agencies" acting to produce degeneration of the aorta, would be more likely to affect the innermost layers of the media than the other portions, because of their poorer blood supply. These deleterious agencies may be toxic or metabolic in character or due to any other cause which will lead to atherosclerosis.<sup>4</sup> Peery<sup>5</sup> reports a case of dissecting aneurysm of the aorta which was probably of rheumatic origin in a 22 year old Negress. In our patient no sclerotic changes were noted in the vasa vasorum.

Most observers, however, are of the opinion that, irrespective of the underlying cause, a sudden exertion in a hypertensive individual increases the blood pressure sufficiently to produce a break in the weakened intima and permits the blood to extravasate rapidly into the diseased media. The extravasated blood may stop at any point in the wall of the descending aorta or burrow its way down into the wall of the iliac vessels or travel upwards to the carotids. Another break usually occurs, from a few moments to many days later, this time in the outer

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coat of the vessel, and the patient dies almost immediately from exsanguination. The exsanguinated blood may accumulate within the pericardial, pleural or peritoneal cavities. In about 15 per cent of the cases the second break occurs at another point in the intima, thereby forming a canal within the aortic wall which often becomes lined by endothelial cells, the so-called "double-barrelled aorta," and the patient may live for many years to die of some other disease. Shennan<sup>6</sup> reported one case of dissecting aneurysm of the aorta which healed completely with obliteration of the sac, the patient subsequently dying from a second dissecting aneurysm.

Males are apparently affected twice as frequently as females. According to Shennan this is true up to 70 years of age because during this period males are more subjected to the stress of life. After 70 years of age the condition is found relatively more frequently in females.

The symptoms are most dramatic. During exertion the patient experiences sudden acute pain in the chest which may be agonizing and tearing in character, almost immediately followed by shock. This pain may last from a few minutes to a number of hours. At times the pain radiates to the back or to the anterior chest wall. Occasionally the pain is located in the epigastrium with radiation to the back thus simulating a perforating peptic ulcer. In our patient the chief symptom was pain in the epigastrium which radiated posteriorly, and which simulated the pain of perforating peptic ulcer.

#### CASE REPORT

The patient, M. J., a white male, 54 years of age, was admitted to the Beth-El Hospital on October 8, 1937 complaining of constant pain in the epigastric region of one week's duration. The pain was severe, unremitting and radiated directly to the back. It was not relieved by alkalies, food or small doses of morphine, and became progressively worse until the day of admission. During this time the patient had experienced constant nausea but had vomited only once on the day of admission immediately following a meal of milk and cream. There was no hematemesis or melena.

*Previous History:* For eight years the patient had suffered from gastric disturbances for which he had been treated by private physicians and at two different hospitals. Each time the discharge diagnosis was peptic ulcer. Until a week before admission each episode of epigastric pain was relieved by food and soda. Diarrhea, constipation, vomiting, tarry stools and hematemesis were never present.

*Physical Examination:* The patient appeared to be well nourished. The head and upper chest were somewhat flushed. The temperature was 101° Fahrenheit. The eyes, ears, nose and mouth presented no abnormal findings.

*Lungs:* There was dullness over both bases, more marked on the left side posteriorly; a few crepitant râles were heard in the left base in the axillary region.

The heart did not appear to be enlarged; the rate was rapid (100 beats per minute); the sounds were of fair quality; no murmurs were heard. The blood pressure was 190 millimeters of mercury systolic and 110 millimeters diastolic.

*Abdomen:* There was marked tenderness in the mid-epigastrium towards the right of the median line; tenderness was also elicited over the twelfth dorsal vertebra posteriorly; the spleen was not palpable; the liver edge was just below the costal margin; no masses were felt.

Because of the history of previous attacks and the roentgenologic findings at the various hospitals where the patient had been treated, the location and radiation of the pain which until the present attack had been relieved by food and soda, and the marked tenderness in the epigastric region which was elicited at the time of the examination,

the diagnosis of peptic ulcer was apparently confirmed. The acuteness and steady persistence of the pain during the present attack, as well as the failure of food and alkali to afford subjective relief, gave rise to the impression that the ulcer was penetrating posteriorly, probably into the pancreas.

*Laboratory Findings:* Blood Count: Red blood cells were 5,200,000 per cubic millimeter; white blood cells were 10,000 per cubic millimeter; hemoglobin was 95 per cent. The differential leukocyte count was as follows: 10 staff cells; 64 segmented polymorphonuclear cells; 4 eosinophiles; 2 monocytes and 20 small lymphocytes. The urine showed no abnormal findings. The blood chemistry showed glucose 107 mg. per cent; urea nitrogen 27.5 mg. per cent; creatinine 1.5 mg. per cent. The blood Wassermann reaction was negative.

The gastric analysis showed the presence of free hydrochloric acid 10° in only one of three fractional specimens. The combined acid reached 30°.

Examination of the feces for occult blood was negative.

*Course:* On October 10 the patient was still complaining of pain in the epigastrium which radiated to the back, although he was receiving Tr. belladonna 10 minims and Tr. opium 5 minims every four hours. The temperature had risen to 103.5° Fahrenheit. Marked tenderness in the epigastrium was still present. On October 11, the pain in the epigastrium with its radiation to the back became so severe and the tenderness so marked that a perforation of the ulcer posteriorly was feared and a surgical opinion was requested. The patient was too ill to undergo a roentgenologic investigation to confirm the diagnosis of peptic ulcer.

The surgical opinion was as follows: "The patient had suffered from several episodes of epigastric pain lasting for several months at a time, which were eventually relieved by treatment. Roentgenologic examination at different times both privately and at various hospitals suggested the presence of a duodenal lesion. During the past 10 days the patient had suffered from continuous excruciating pain in the epigastrium which radiated to the back, producing at times difficulty in breathing due to diaphragmatic fixation. No definite mass can be elicited in the abdomen, nor is the epigastric tenderness aggravated by palpation. Advise continued sedation to be followed by a roentgenologic study of the stomach which is to be followed by an operation."

Because of the intensity of the pain morphine sulphate, gr.  $\frac{1}{4}$  by hypodermic injection, was then added to the medication as needed.

On October 14 the patient still complained of the epigastric pain which radiated to the back though much milder in intensity.

The next day the patient was more comfortable, was able to take more nourishment, and had a bowel movement following a soap suds enema.

By October 17 the pain had been so much relieved that the morphine was discontinued and the patient prepared for a roentgenologic study of the stomach and duodenum. This was done on the following day. A thorough study by the roentgenologic department failed to reveal any evidence of gastric or duodenal ulcer.

On October 21 the patient still complained of an uncomfortable feeling in the epigastrium, and it was decided to refluoroscope the patient, which was done the same day. At this time the stomach and duodenum were again found to be normal, showing no evidence of a gastric or duodenal ulcer. However, fluoroscopy of the chest revealed a fusiform pulsating dilatation of the entire descending aorta. A roentgenologic film of the chest confirmed the finding of the fusiform dilatation of the aorta (figure 1). A dissecting aneurysm of the aorta was then suspected.

On October 23 the patient stated that he was somewhat improved but still complained of slight discomfort in the epigastrium and posteriorly between both shoulders. An electrocardiogram was ordered but could not be taken in time.

On the morning of October 25 the patient declared that he felt "fairly well" and was able to eat. At 7:15 p.m. of the same day while the patient was on the bed pan he suddenly turned white, vomited, gasped for breath, and expired.

From the third day after admission to time of death the temperature fluctuated between 100 and 102° Fahrenheit. Only twice during this time did it fall to 99°.



FIG. 1. Six foot roentgenogram of chest showing fusiform dilatation of the descending aorta. The trachea deviated toward the right. No enlargement of the heart.

#### NECROPSY

*Chest:* The level of the leaves of the diaphragm was not unduly displaced. The trachea was deviated to the right. The heart was pushed over the left, the apex lying behind the sternum. The left pleural cavity contained about a liter of sanguinous serum and several huge blood clots. The right pleural cavity was free.

*Lungs:* The pleural surfaces were glistening, showing evidence of anthracosis. The lungs were hypercrepitant throughout and pitted on pressure. The edges could be expressed to paper thinness. At the apices there were several thin walled emphysematous blebs. On section the lungs were dry, the right lung presented a reddish gray appearance, whereas the left lung was of a very pale gray. The trachea and bronchi were clear. The hilar lymph nodes showed no evidence of disease. The pulmonary vessels also showed no changes.

*Heart:* There was no increase in the pericardial fluid. The pericardium itself was glistening. The right heart was dilated, and the left ventricular musculature was moderately hypertrophied. The myocardium was pale, reddish brown in color and of fairly good texture. The heart chambers were empty. The valves presented no pathologic changes. The coronary arteries showed a moderate degree of intimal lipid deposition and calcification, without seriously encroaching upon the lumen. The ascending aorta showed little atherosclerotic change but some loss of elasticity. In the arch of the aorta distal to the openings of the left subclavian and left carotid arteries there was a transverse linear break encircling the posterior half of the aorta and extending through the intima into the media. This permitted the escape of blood from within the lumen of the aorta into the wall out beyond the media. The aorta in its thoracic portion presented a blood clot, lamellated and partially organized, about three centimeters thick, lying outside the media and pushing both intima and media into folds into the lumen (figure 2). At the region of the break in the arch blood was present in the loose perivascular tissue resting against the very thin parietal pleura of the apical portion of the left chest. On its pulmonary aspect this pleura was coated with blood and fibrin. Both the thoracic and abdominal portions of the aorta had lost much of their elasticity and contained many lipid plaques some of which were calcified. An area of atheromatous softening involving both the intima and the media was present near the break in the arch of the aorta. The renal, splenic, and gastric arteries, and some smaller arteries showed a moderate degree of arteriosclerosis.

*Gastrointestinal Tract:* The esophagus presented no abnormal changes. The stomach was markedly distended, so that the rugae were almost effaced. The mucosa was congested but presented no evidence of recent or old ulceration either in the stomach or in the duodenum. The intestines were moderately distended. The colon contained bile-stained feces in which barium was recognized. Congenital cysts were found both in the kidney and in the liver within the region of the gall-bladder. Another cyst one centimeter in diameter was found in the spleen. No changes were noted in the portal and hepatic vessels.

#### MICROSCOPIC EXAMINATION

*Aorta:* A section was taken from the margins of the break and hemorrhage. The intima was markedly and irregularly thickened, and was composed of dense hyalinized tissue with lipid deposits. Its endothelium was broken. A vascularization with some round cell infiltration was noted. The media was thinned in places and contained considerable fibrous tissue which was vascularized. No perivascular cellular infiltration was noted in the adventitia.

*Aorta:* Section through the aneurysm. There was an organized blood clot within the outer part of the media. The adventitia was thickened and fibrosed and contained considerable granulation tissue with round cell infiltration. The outer portion of the media near the blood clot showed degenerative changes.

Elastica-Van Gieson stains on sections of the aorta showed that the aneurysmal dissection took place in the outer portion of the media; a few elastic fibers were seen along the adventitial border of the mass of blood. Some sections showed a severe degree of atherosclerosis and the irregularly thickened intima with considerable hyalinized fibrous tissue. At this point the media showed fragmentation of the elastica and in places fibrous scarring with total replacement of elastic fibers together with vascularization. In such areas, particularly those taken through the point of rupture, there was considerable necrosis of the intima, with necrotic lipid containing cells admixed with necrotic tissue. In the underlying adventitia there was a rather marked leukocytic infiltration which was also noted near the necrotic intima. None

of the vasa vasorum examined showed endarteritic changes; and whereas in some places perivasasavascular lymphocytic infiltration was present, this appeared to be only part of a general cellular infiltration, which included numerous polymorphonuclear cells. There was no associated intimal cellular hyperplasia of the affected vessels.

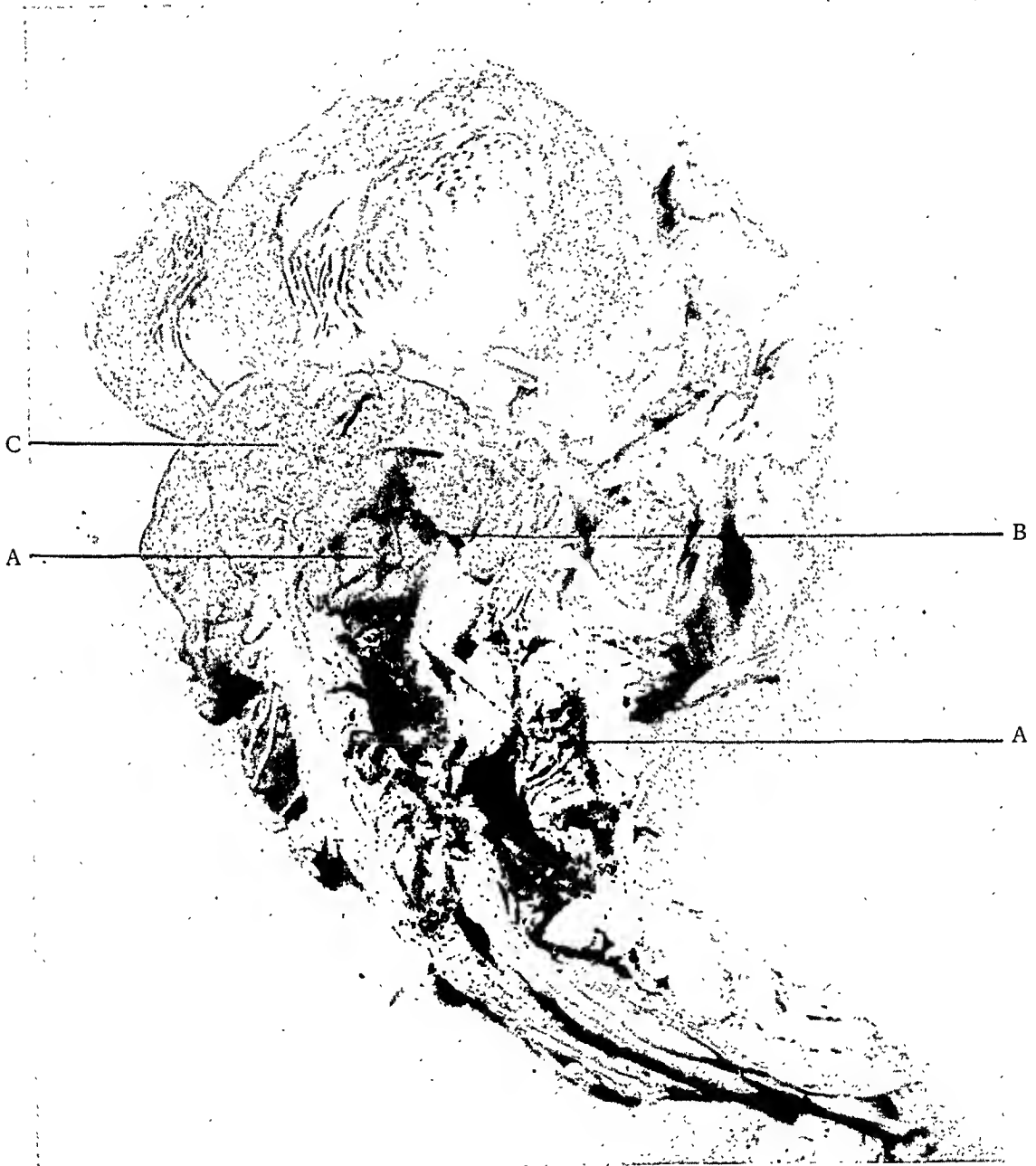


FIG. 2. Heart and aorta. Note the blood clot dissecting in the outer wall of the aorta (*A*). The clot communicates with the aortic lumen through an opening at *B*. At *C* is the extra-aortic blood clot in the left pleural cavity.

## COMMENT

With the large number of patients suffering from hypertension and arteriosclerosis it is most probable that the incidence of dissecting aneurysm of the aorta is greater than one is led to believe by the number of cases reported. Most of these patients presumably die of cardiac failure or coronary artery disease and do not come to autopsy. The true diagnosis will be arrived at only if the symptoms are carefully analyzed and dissecting aneurysm of the aorta is kept in mind.

The sudden onset of agonizing pain in the chest which often radiates to the back in a patient suffering from hypertension, without evidence of acute cardiac or pulmonary disease, should suggest the diagnosis of dissecting aneurysm of the aorta. If the patient lives long enough a roentgenogram of the chest will reveal a fusiform widening of the aorta which on fluoroscopy may or may not be seen to pulsate.

In a number of cases reported by Shennan, Peery and others, and in our case, the outstanding symptom was severe pain in the epigastrium simulating ulcer pain. Indeed a few such patients have been operated upon for peptic ulcer which was not found.

A number of significant findings in our case are of interest. Microscopically the site of primary rupture showed evidence of regeneration and vascularization which bears out the clinical evidence that some time elapsed between the primary intimal rupture and the secondary external rupture. According to the history the interval was at least 25 days, which is much longer than in the average case.

The vasa vasorum were not involved. This would tend to prove that the media, especially the inner layers, may be affected by degeneration due to arteriosclerotic changes in the intima and not necessarily by previous disease of the vasa vasorum as was suggested by Tyson.<sup>3</sup>

Of great clinical interest, however, is the fact that for eight years prior to his last illness the patient suffered from gastric symptoms which led to the diagnosis of peptic ulcer for which he was treated. However, the roentgenologic examination during his last illness and the necropsy findings failed to reveal any evidence of a recent or healed gastric or duodenal ulcer. The dissecting aneurysm of the aorta could be ruled out as a cause of the long standing gastric symptoms because of its recent onset, no more than seven days before the patient was admitted to the hospital. The absence of any pathologic lesions in the liver, gall-bladder, intestines and appendix, eliminates these organs as a cause for the ulcer symptoms.

However, sclerotic changes were noted in the gastric, splenic, and renal arteries. It has been known for a long time that sclerotic changes in the celiac axis or its branches may give rise to gastric symptoms, even to hemorrhage. It is possible that the peptic ulcer symptoms from which our patient suffered for eight years prior to his last illness must have been caused by the arteriosclerotic changes in the branches of the celiac axis.

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## TRAUMATIC CHYLOTHORAX: CASE REPORT \*

By JOSEPH GORDON, M.D., *Ray Brook, New York*

TRAUMATIC chylothorax is sufficiently uncommon to warrant an additional case report in the literature. The case here reported is the first instance of this condition observed in a series of 3,000 admissions to the tuberculosis division of this institution during a period of 10 years. One might justifiably expect that such cases, if they did occur at all frequently, would often find their way into an institution where diseases of the chest make up a major portion of the admissions.

### CASE REPORT

N. O., a white male, aged 31 years, was admitted on August 11, 1937 on the advice of his family physician. The patient had been treated for an upper respiratory infection. In the course of somewhat irregular treatment over six months, fluid was noted in the right chest and on thoracentesis it was seen as a thick creamy fluid. Accordingly, hospitalization was advised by the family physician for treatment of a pleural effusion. The patient was a native of Holland and had worked as an electrician. The past history was non-contributory, since except for the usual childhood diseases, he had always been in good health. The family history was irrelevant. There was no family or contact history of tuberculosis or familial disease. The present illness began about seven months prior to admission with a "cold in the chest" which persisted. He then developed pain over the sternum which continued for several weeks. Only slight improvement was experienced after a course of "injections" for the cold. Some weeks later he again consulted his family physician because the patient noted that he was having fever and was losing weight. Fluid was found in the chest at this time. The patient was confined to bed for three weeks before admission to the hospital.

Physical examination revealed a fairly well nourished and developed white male. He did not appear acutely ill. Some pallor was observed. The examination was negative save for the chest findings. Expansion was limited on the right and resonance was impaired over the lower half of the chest. Breath sounds were diminished to absent in this area and there was decreased tactile and vocal fremitus. A few moist râles were heard posteriorly. The left lung was clear. Examination of the abdomen was negative for masses or tenderness.

*Laboratory Data:* Urine: essentially negative. Blood: red blood cells 5,390,000, hemoglobin 105 per cent, white blood cells 8,500, polymorphonuclears 56 per cent, lymphocytes 42 per cent, eosinophiles 2 per cent. Wassermann and Kahn tests negative. Blood cholesterol 145 mg. per cent. *Tuberculin test:* two plus. *Sedimentation rate* (Cutler method): 2 mm. in one hour. Repeated sputa examinations including smears, concentrates, cultures, guinea pig inoculations; and likewise gastric aspirate

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examinations were negative for the tubercle bacillus. Chest fluid: thick, creamy, yellow in color, specific gravity, 1.025, cells predominantly lymphocytes; no organisms.

*Roentgen-ray: 1. Chest:* A homogeneous density was present obliterating the right leaf of the diaphragm and extending up to the level of the third rib. Pulmonic markings were clean cut above on the right and throughout the left lung.

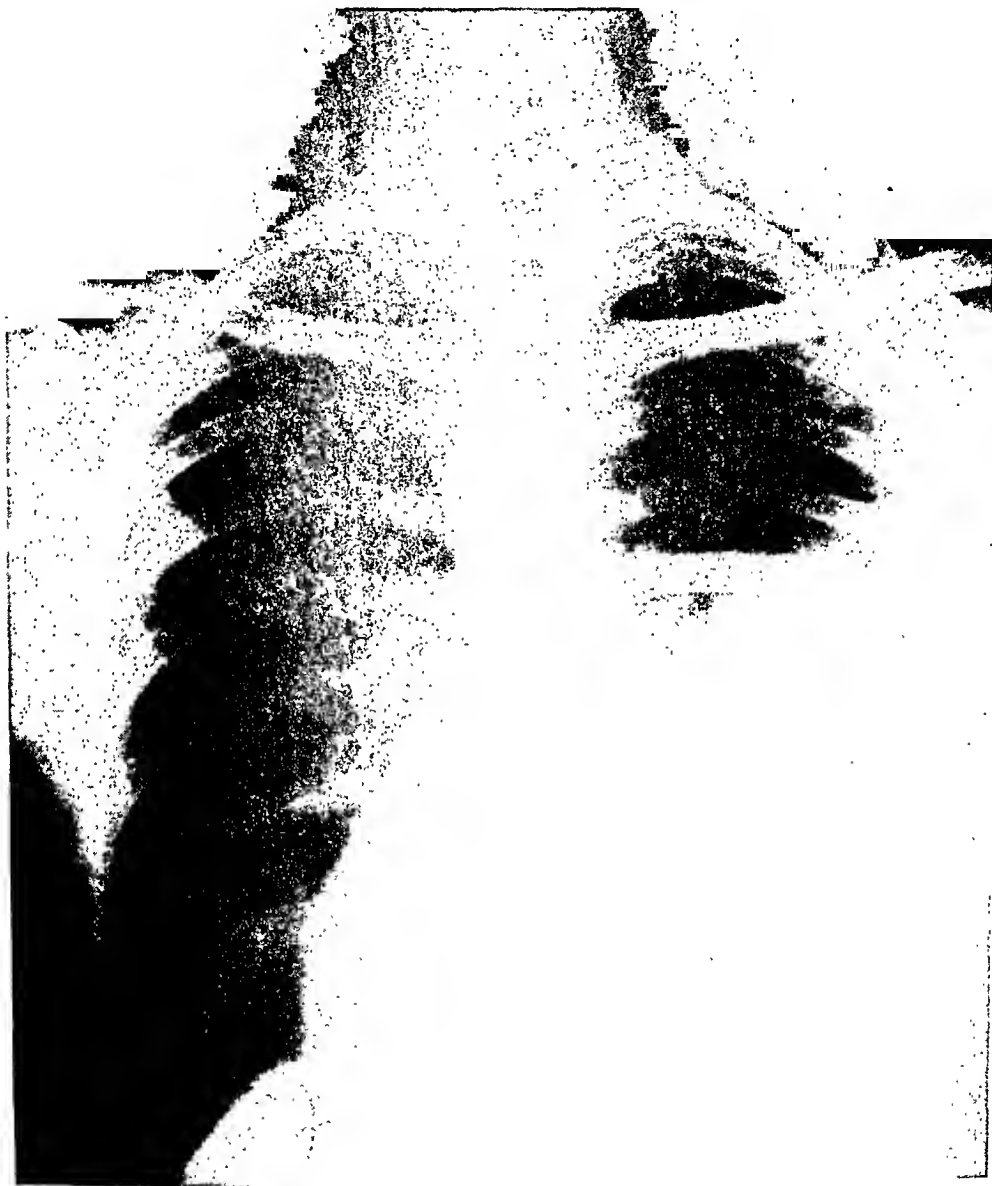


FIG. 1. Admission roentgen-ray showing chylous effusion on the right side.

*2. Abdomen:* Kidney shadows about normal in size. Their lower borders were normal in size and position; the upper border of the right kidney merged with the density in the right thorax.

A tentative diagnosis of pleural effusion was made. The etiological factor on the basis of the history of cough, cold, fever, night sweats with loss of weight, was

considered as tuberculosis. With the absence of organisms and rapid recurrence of this milky fluid, chylothorax was suspected. Fluid in amounts ranging from 950 c.c. to 1500 c.c. was removed on frequent occasions. Its character was unchanged at all times. The fluid was stained with sudan III and fat globules were found on micro-

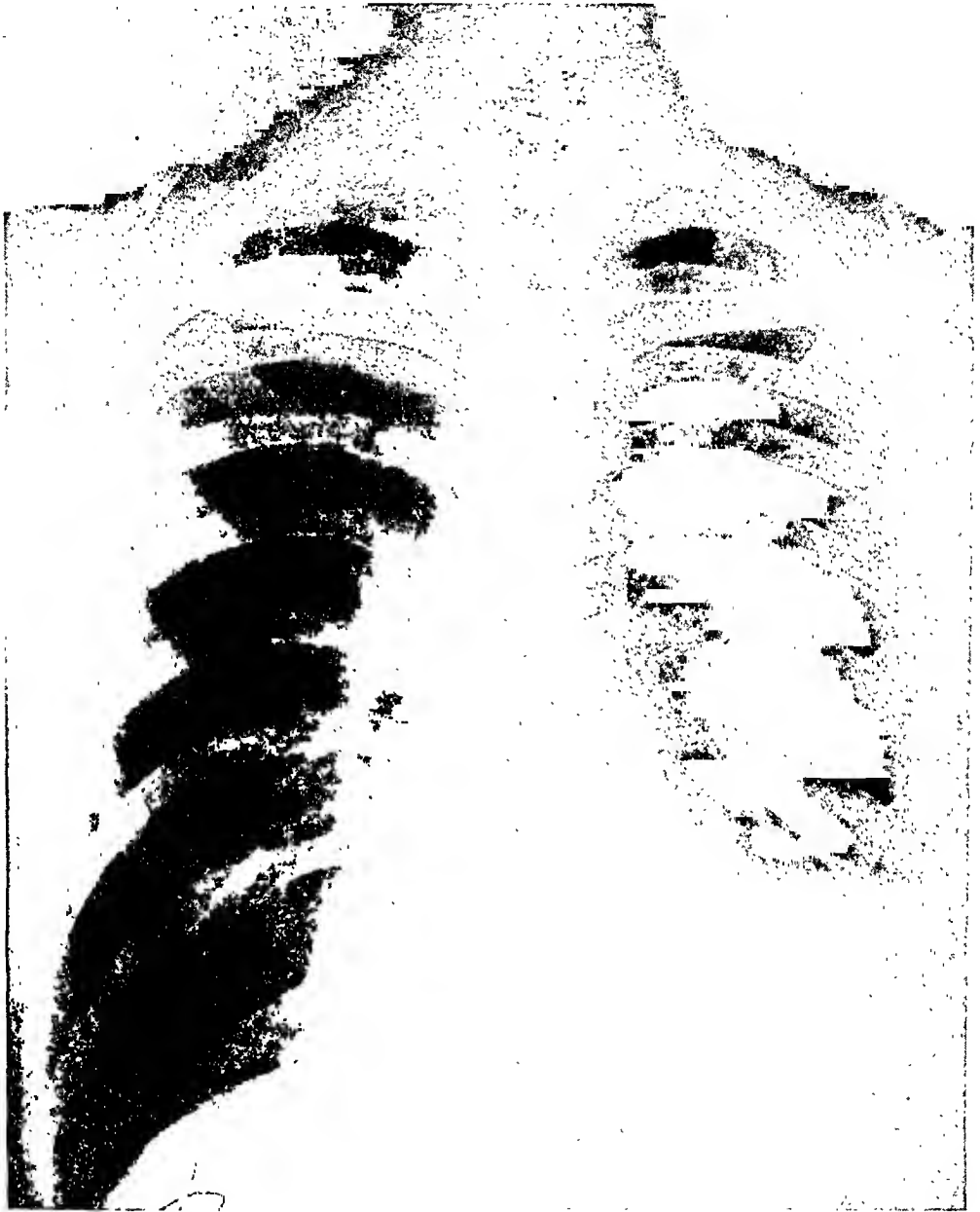


FIG. 2. Roentgen-ray following almost complete evacuation of fluid from chest showing normal lung fields.

scopic examination. On August 13, 1937 the fat content, by the method of Babcock, was reported as 1 per cent. Repeated examinations of the fluid for organisms, both pyogenic and acid-fast, were negative on smears, cultures, guinea pig and rabbit inoculations. Examination of the fluid for possible tumor cells was negative. Further

analyses for fat content showed 3 per cent on two occasions. Following a high fat diet for one week the fluid was reported as containing 4.8 per cent fat. This was then followed by one week on a fat-free diet. The analysis again showed 3 per cent.

*Course of Treatment in Hospital:* The patient was put on absolute bed rest and received symptomatic treatment including diet and chest aspirations when indicated. Bi-weekly aspirations were done for three months when the fluid began to show a decreased tendency to formation. The chest was irrigated with a 1:3300 saline solution of azochloramid. This was followed by a slight febrile reaction which lasted for five days, ranging between 101–103° F. The patient gradually improved and was allowed out of bed. From an admission weight of 157 pounds his weight increased to a present weight of 174 pounds. Although the fluid is extremely slow in reforming, requiring aspiration once a month, the patient is still being kept under observation.

When the diagnosis of chylothorax was made, it was necessary to determine the etiological factor. No history of an illness of any sort could be obtained. The several factors which might give rise to chylothorax as outlined by McNab<sup>1</sup> (table below) were carefully considered.

#### CAUSE OF CHYLOTHORAX

*Table from McNab<sup>1</sup>*

- I. Trauma
  1. Closed trauma
    - (a) Without fracture of bones
    - (b) Accompanied by fractured ribs, clavicle or vertebrae
  2. Operative wounds
    - (a) Duct severed
    - (b) One or more terminals severed
  3. Gunshot or stab wounds
- II. New growths and granulomata outside duct: carcinoma, lymphosarcoma, tuberculous glands.
- III. Thrombosis of left subclavian vein
- IV. New growth within duct
- V. Perforating lymphangitis
- VI. Aneurysm of duct
- VII. Cirrhosis of liver
- VIII. Filaria

After reviewing with the patient his past history, it was found that about a month prior to the onset of his present illness he received a rather severe blow on the chest accidentally during his work. Although the blow was rather forceful and caused some momentary discomfort he continued with his work. In the absence of any other explanatory factor, it was hypothesized that an injury to the thoracic duct was sustained at that time. This was perhaps precipitously manifested when the upper respiratory infection, associated with severe coughing, completed the rupture of the duct. Obviously, this theory is grossly lacking in proof, nor can proof of the etiology be obtained from a patient who is recovering from his injury. In the absence of evidence of another cause it was felt that trauma was the most likely etiologic factor in the thoracic duct injury.

In 1931 Van Nuys<sup>2</sup> was able to collect 66 cases of chylothorax of all types. Apparently involvement of the peritoneum is somewhat more common than the pleura, occurring about twice as often.

Shackelford and Fisher<sup>3</sup> recently carefully reviewed 41 cases of traumatic chylothorax from the literature while reporting 2 of their own. Injuries to the chest giving rise to chylothorax were numerically tabulated as follows:

## CAUSES OF TRAUMATIC CHYLOTHORAX

Crushing injuries .....	17
Wounds (bullet and stab) .....	8
Fall from height .....	6
Blow on chest .....	5
Thrown against front seat of auto .....	4
Hyperextension .....	1
	<hr/> 41

Crushing injuries were the most predominant causative agents. Great violence is by no means essential, however, nor is it necessary to sustain injury to the bony skeleton.

The manner whereby the thoracic duct is injured is not always clearly ascertained. Where nearby structures such as the clavicle, ribs or vertebrae are injured, the close proximity of the duct explains the likelihood of its being torn or even perforated by a bony fragment. The manner of injury is also obvious in cases of gunshot or stab wound. One of the earlier case reports was made by Finkelstein<sup>4</sup> in 1901. Here too was mentioned incidental injury to the thoracic duct in surgical operations in the neck region, as in the removal of a cervical tumor. Sudden changes in hydrostatic pressure have been offered as a possible explanation of rupture of the thoracic duct in other instances.

The possibility of injury to the duct to a lesser degree than would cause its rupture seems reasonable. A secondary factor of severe cough occurring sometime later might completely rupture the duct by a sudden change in hydrostatic pressure. This theoretical explanation suggested itself in the above case. Although there is a latent period of one month, an even longer period was noted in the case report of Beatty.<sup>5</sup> In this case an automobile accident occurred in June 1928 and symptoms developed in January 1935 following a "cold." Here too the latent period between traumatic injury and the appearance of definite symptoms is only conjecture.

In the entire series of 41 collected cases of traumatic chylothorax, the distribution as to the side of the chest in which the fluid was found, is shown in the following table (Shackelford and Fisher):

## LOCATION OF EFFUSION

	Open Injuries	Closed Injuries	Total
Left chylothorax	9	5	14
Right chylothorax	2	18	20
Right chylothorax with chylous ascites	0	1	1
Bilateral chylothorax	1	4	5
Bilateral chylothorax with chylous ascites	0	1	1
Left chylothorax with chylous ascites	0	0	0
	<hr/> 12	<hr/> 29	<hr/> 41

The appearance of the chylous fluid on one or the other side of the thorax seems to bear some relation to the location of the perforation in the anatomical course of the duct. It enters the thorax through the aortic hiatus, somewhat on the right side and gradually inclines to the left, crossing at about the level of the fifth dorsal vertebra. Here it reaches the superior mediastinal cavity when the ascent continues on the left into the neck. The duct empties into the venous system at the angle of junction of the left subclavian vein with the left internal

jugular vein. Occasionally it may divide into two branches in the thorax. It would therefore seem that injuries which occur low down in the course of the thoracic duct would account for the effusion presenting itself on the right side; those occurring higher up would explain the presence of the chylous fluid on the left side. In several of the autopsied cases the location of the perforation of the duct coincided with the presence of the fluid on the right or left side of the chest. However, in Heppner's<sup>6</sup> case the perforation was seen 2.5 cm. above the diaphragm and chyle appeared not only in the abdominal cavity, but also in both pleural spaces.

The thoracic duct lies extrapleurally with relation to the covering of the lungs. In instances where a perforating injury also includes the parietal pleura, leakage into the pleural cavity is obvious. When the rupture is only of the duct itself, entrance into the pleural cavity probably occurs by leakage through the pleura, or through a perforation of the pleura caused by local pressure necrosis. A satisfactory explanation for bilateral effusion is still lacking except on a similar basis.

The diagnosis is dependent upon thoracentesis and careful examination of the fluid. Lillie and Fox<sup>7</sup> mention the striking clinical features as: (1) the latent period before the onset of the symptoms; (2) the rapid re-accumulation of the fluid within the chest after aspiration; (3) the gradual progressive emaciation which frequently ends in death. According to Wallis and Schölberg<sup>8</sup> the specific gravity of true chylous fluid should be above 1.012. In this case the specific gravity was 1.025. Microscopic examination of the fluid for fat droplets which take the sudan III stain is confirmatory and a quantitative analysis for the percentage of fat present rules out the possibility of pseudo-chylous fluid. In addition, a further confirmatory test was added by noting an increase in the amount of fat in the pleural fluid following the ingestion of a high fat diet.

That chyle is essential for the maintenance of nutrition is reasonably well established. The normal flow of lymph from the thoracic duct is from 130 to 195 c.c. per hour. It might be well to point out at this time that the patient showed a weight loss on a fat-free diet, although calorically the diet was apparently adequate. After returning to a regular diet the weight gain as previously evidenced was rather steady and well maintained.

Of the 41 reported cases, 19 died, indicating that the mortality in traumatic chylothorax is strikingly high. Aside from shock and severe injury in these cases, the fact that treatment is non-specific, varied and generally unsatisfactory may be partly responsible for this.

Treatment may be classified under three general headings: (1) Drainage (either by thoracentesis or rib resection); (2) diet (usually low fat); (3) intravenous or oral administration of chyle. Combinations of 1 with 2 or 3 have also been used in certain cases. Rectal feeding was suggested by Hall and Morgan,<sup>9</sup> the rationale being that the lymphatics in this region would absorb the foodstuff and enter the superficial lymph system, thereby circumventing the thoracic duct. Van Nuys<sup>2</sup> used high voltage roentgen-ray in the region of the lower mediastinum in addition to aspiration. Operative repair or ligation of the duct in such cases is not feasible for two reasons: (1) generally the patient is in poor condition; (2) the site of rupture of the duct is rather inaccessible technically. Repair of the thoracic duct in the neck region, however, has met with success in the instances when it was used.<sup>10, 11</sup>

The highest percentage of reported recoveries occurred in those cases treated by thoracentesis alone. This was the elected method of treatment in the above case. The ultimate outcome cannot be accurately prognosticated, but the present indications are that it will be favorable.

#### SUMMARY AND CONCLUSIONS

1. A case of chylothorax of likely traumatic origin is presented.
2. The mechanisms responsible for rupture of the thoracic duct are cited. In the above case there seemed to be a combination of two etiological factors.
3. The diagnosis is entirely dependent upon thoracentesis with examination of the fluid for fat droplets and other studies.
4. The high mortality is mentioned and the methods of treatment enumerated.
5. Repeated thoracentesis evidently yields the best results.
6. An apparent favorable outcome in this case has been obtained by the above-mentioned method.

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## EDITORIALS

### *THE TWENTY-FOURTH ANNUAL SESSION*

The Twenty-fourth Annual Session of the American College of Physicians at Cleveland not only drew a very large attendance of physicians but richly repaid them for coming. The program of General Sessions, Morning Lectures and Panel Discussions had a consistently large audience. Indeed the latter were so popular that many who applied late were unable to obtain tickets.

The program provided by the hospitals and medical schools as ably organized by the General Chairman, Dr. Karsner, was enthusiastically praised. In addition to all these intellectual advantages offered by the meeting, the members of the College will remember with pleasure the cordial greetings given to the College by the medical profession of this splendid medical center, Cleveland.

### *BLOOD FOR BLOOD CULTURES*

The striking advances in specific chemotherapy have increased the importance of isolating the etiologic organism in any acute infection. This may be possible at times by surface cultures or by bacteriologic studies of sputum, urine, spinal fluid, or exudates in the pleura, joint cavities, etc. There is, however, in some of these instances, especially in surface throat cultures, sputum cultures and urine cultures, a degree of uncertainty as to whether the organisms obtained are identical with those causing the constitutional symptoms. Since bacteria in the blood stream may be assumed to be etiologic agents, and since their presence there moreover indicates a dangerous invasion of the whole body, the use of the method of blood culture is universal in all cases of sepsis.

It may be questioned, however, whether the routine method of obtaining blood for blood culture from a vein in the arm is always the most delicate method of determining an invasion of the blood stream or of identifying the pathogenic organism for therapeutic purposes. In the case of thrombophlebitic sepsis it has been shown (Friedemann<sup>1</sup>) that blood taken from a vein directly draining the focus of infection contains many more organisms than the venous blood as sampled from another area. This is due in part to the great dispersion of the bacteria in the general blood stream, in part to their destruction, and in part to the filtering effects of the capillary beds through which they may pass. Bacteria from the intestinal tract, for example, must pass the capillary bed of the liver, that of the lung, and that of the forearm or hand before they will reach the veins of the elbow from which blood is taken for culture. Organisms from an infection at the

<sup>1</sup> FRIEDEMANN, U.: Bakteriologische Topodiagnostik der Sepsis, München. med. Wchnschr., 1929, lxxvi, 1323-1327.



periphery of the body will have to pass the capillaries of the lungs and of the forearm or hand before they reach the elbow veins. If the infection spreads by lymph channels there will be further filtering out by the lymphoid tissues before the venous system is reached. Bacteria causing lung infections which invade venous channels directly have, however, only the peripheral capillary bed to pass before reaching the arm veins.

It would seem reasonable, therefore, in serious infections at the periphery to utilize whenever feasible a vein draining the infected area as a source of blood for culture. The question of whether in pneumonia arterial blood cultures would possess an advantage over venous cultures sufficient to outweigh the greater technical difficulty and painfulness of the arterial puncture remains unsettled. In a group of cases of septicemia Bock<sup>2</sup> found arterial cultures positive in 15 per cent more of the cases than venous cultures. The method seems worthy of further trial.

<sup>2</sup> Bock, H. E.: Über den Wert der bakteriologischen Sternalmarkuntersuchung, *Klin. Wchnschr.*, Berlin, 1939, xviii, 162-165.

## REVIEWS

*Lehrbuch Der Augenheilkunde.* By DR. ERNST FUCHS. Enlarged and improved by new work of DR. ADALBERT FUCHS. 917 pages; 25.75 cm. X 18 cm. Franz Deuticke, Vienna. 1939. Marks 27.

It is indeed a pleasure to review a new sixteenth German edition of Dr. Fuchs' well-known textbook on ophthalmology. This work was first published in July, 1889 and has had ten English editions, the last appearing in 1933.

The work consists of 904 pages including the index, with 362 illustrations, a large number of which are colored drawings of pathological lesions, and with 5 colored plates.

The author divides the work into five parts. The first consists of a chapter on physiology of the eye, one upon the general pathology and one upon general therapy. The second part has a chapter on objective examination of the eye and one upon functional testing. The third part takes up the various diseases of the eye with chapters dealing with the conjunctiva, cornea, sclera, uvea (anatomy and physiology), iris and ciliary bodies, choroid, glaucoma, lens, vitreous, retina, optic nerve, lids, lacrymal apparatus, motor anomalies and the orbit. The fourth part deals with refractive errors and their correction, and consists of six chapters, the first dealing with lenses, the second with the optical mechanism of the normal eye, the third with myopia, the fourth with hyperopia, the fifth with astigmatism and the sixth with anomalies of accommodation. The fifth part takes up the operations upon the eye. The first chapter describes the general preparations of both instruments and the patient, the second considers operations upon the bulb, and the third takes up operations upon the adnexae.

It seems that the work has been brought well up to date, and the valuable illustrations of pathological specimens by the younger Fuchs have added materially to its value.

The reviewer wishes to criticize the placing of the colored plates at the end of the book. In his opinion, it would be much more effective to have each one placed in the proper relation to the text.

We hope that this sixteenth edition also, will be translated into English and thereby become available to the large American group of ophthalmologists and internists.

C. A. C.

*Classic Descriptions of Disease.* Second Edition. By RALPH H. MAJOR, M.D. 716 pages; 25.5 cm. X 17.5 cm. Charles C. Thomas, Springfield. 1939. \$5.50.

In these days of practical teaching we are too often apt to forget epoch making observations and classic accounts of disease which can so enliven the background of any clinical subject. Dr. Major has provided an excellent source book of such original contributions to medicine which have served him in his teaching. The work is similar to those recently appearing in the fields of pathology, obstetrics and physiology. The author states that his selection of authors in this collection has been influenced by personal taste and the fact that some diseases have more interesting and extended histories than others. He further states that his selections deal in the main with clinical medicine, and that the fields of bacteriology, therapeutics and neurology have been omitted.

The book is composed of 403 selections from 190 authors arranged in 10 main sections with the following headings: infectious diseases, diseases of metabolism, lead poisoning, diseases of the circulatory system, diseases of the blood, kidney diseases, respiratory diseases, deficiency diseases, allergic diseases, and diseases of the digestive

tract. The author states that in this second edition there are new sections on malaria and yellow fever, and that many of the biographical sketches have been rewritten and the index revised and enlarged.

The material in the book is arranged in the form of succinct biographical sketches of both ancient and modern physicians followed by extracts from the works of these men who have contributed to fundamental knowledge in clinical medicine. These extracts in most instances have been translated (where necessary) and paragraphed by the author with considerable reduction in reading effort as the result. Numerous reproductions of portraits, illustrations and pages from classic works lend color to the book. There is an adequate index and the print is clear. The biographical references are given throughout the book.

Upon finishing the book the reader is determined not to close it permanently but to place it on his reference shelf for frequent use.

J. E. S.

*Medicine in the Outpatient Department. An Introductory Handbook.* By WINTHROP WETHERBEE, JR., M.D. 111 pages; 15.5 X 12 cm. Paul B. Hoeber, Inc., New York. 1938. Price, \$1.00.

If the third year student masters the information and point of view contained in "Medicine in the Outpatient Department," he would indeed be well prepared to take advantage of his dispensary medical course. The author suggests certain simplifications in history taking and physical examination which are necessary because of the usual lack of time for examination and instruction in the outpatient department of a large city hospital.

The reviewer feels, however, that it is unfortunate that students must be introduced to clinical medicine with the aid of shortcuts, but as long as medical instruction in the dispensary is given to third year students this book will fill a definite need. It can be highly recommended and should be widely used.

M. S. S.

*Dental Science and Dental Art.* Edited by SAMUEL M. GORDON, Ph.D. 731 pages; 24 X 15 cm. Lea and Febiger, Philadelphia. 1938. Price, \$9.50.

For the internist interested in focal infection, this book will be a mine of information about his favorite subject. The editor and his collaborators herald the "dentistry of tomorrow based on science." Occasionally repetitious and somewhat grandiloquent in style, the book is full of effective diagrams and tables. The newer work on parathyroids and vitamins is included with laudable conservatism. The section on orthodontia has significance in many allied specialties. Dental caries is discussed from many angles with a thorough display of experimental data and photographs. Vincent's infections are thoroughly analyzed, as are many other medical diseases of the mouth. The art of dentistry does not obtrude itself upon the medical reader.

There are full references at the end of each chapter.

C. A.

## COLLEGE NEWS NOTES

### TWENTY-FOURTH ANNUAL SESSION OF THE COLLEGE

The Twenty-fourth Annual Session of the American College of Physicians held in Cleveland, April 1-5, inclusive, 1940, proved to be one of the most successful and most largely attended sessions in the history of the College. There were in attendance physicians from 47 States, Hawaii, Puerto Rico, 8 Provinces of Canada and from Mexico. It is interesting to note that physicians came from 476 different communities. The largest number of registrants was from Ohio, with New York second, Pennsylvania third, Michigan fourth and Illinois fifth. A comparison of attendance for the past four years follows:

	Cleveland (1940)	New Orleans (1939)	New York (1938)	St. Louis (1937)
A. C. P. Members	1,221	896	1,447	877
Guest Physicians	710	525	463	589
Medical Students	116	499	3	414
Visiting Women	262	578	319	210
Exhibitors	223	167	291	201
Other Non-Physicians	25	16	24	30
	2,557	2,681	2,547	2,321

The program of General Sessions and Morning Lectures, as well as that of the Clinics and Panels was acclaimed as among the best arranged by the College. It was particularly noted that the Panels proved exceedingly attractive and that many more members sought admission than facilities would permit.

The technical exhibit, limited in size by intent, represented the highest type exhibit of its kind shown at any medical meeting to date. The College Committee on Exhibits and Advertisements has applied a selective system by which undesirable and irrelevant exhibits are eliminated. Each exhibit was selected because it was particularly representative of the interests of Internal Medicine and its allied specialties. High pressure methods and undesirable tactics were debarred. Here was assembled a group of exhibitors of the highest class, manned by gentlemen of training and courtesy. Especially was there an excellent exhibit of medical books, pharmaceuticals, apparatus and appliances.

At the Convocation on Wednesday evening, April 3, President O. H. Perry Pepper delivered the annual presidential address and Dr. Charles F. Martin, Master and ex-President of the College, Emeritus Dean and Emeritus Professor of Medicine of the McGill University Faculty of Medicine, delivered the Convocational address, an interesting and inspiring review of the development of the College.

The transactions of the Board of Regents and of the Board of Governors, together with an account of the Annual Business Meeting of the College, will be published in a later issue of this journal. However, herewith is published the roster of those inducted into Fellowship at the Convocation April 3, 1940, and the list of elections to Associateship on March 31, 1940.

## ROSTER OF NEWLY ELECTED FELLOWS, 1939-40

Walter Paul Adams.....	Norfolk, Va.
Kenneth Dayton Allison Allen.....	Denver, Colo.
John Arthur Alvarez.....	Houston, Tex.
Harold Cook Atkinson.....	Macon, Ga.
Villairs Thomas Austin.....	Urbana, Ill.
Louis John Bailey.....	Detroit, Mich.
David W. E. Baird.....	Portland, Ore.
Thomas Williams Baker.....	Charlotte, N. C.
M. Herbert Barker.....	Chicago, Ill.
Douglas Davison Baugh.....	Columbus, Miss.
Sim Fields Beam.....	St. Louis, Mo.
Marion Foree Beard.....	Louisville, Ky.
George Erick Bell.....	Wilson, N. C.
Alan Bernstein.....	Baltimore, Md.
Walter Reece Berryhill.....	Chapel Hill, N. C.
Benjamin Jaffee Birk.....	Milwaukee, Wis.
Caryle Bernard Bohner.....	Indianapolis, Ind.
James Loudon Borland.....	Jacksonville, Fla.
Raymond William Brust.....	Philadelphia, Pa.
James Arthur Buchanan.....	Brooklyn, N. Y.
Burdette Jay Buck.....	Hartford, Conn.
Anthony Vandril Cadden.....	Hopemont, W. Va.
Coyne Herbert Campbell.....	Oklahoma City, Okla.
Edward Guy Campbell.....	Memphis, Tenn.
Edward Wyatt Cannady.....	East St. Louis, Ill.
Elmer Theodore Ceder.....	Baltimore, Md. (U. S. P. H. S.)
Charles Thomson Chamberlain.....	Fort Smith, Ark.
Earle MacArthur Chapman.....	Boston, Mass.
Clarence Orion Cheney.....	White Plains, N. Y.
Benjamin Earl Clarke.....	Providence, R. I.
Thomas Alfred Clawson, Jr.....	Salt Lake City, Utah
Arthur Ralph Colwell.....	Evanston, Ill.
Elias Earle Cooley.....	M. C., U. S. Army
Henry Lewis Cooper.....	Denver, Colo.
John Cosgrave Corrigan.....	Fall River, Mass.
Langdon Teachout Crane.....	Detroit, Mich.
Erle Bulla Craven, Jr.....	Lexington, N. C.
Lloyd Freeman Craver.....	New York, N. Y.
Jacob Antrim Crellin.....	Philadelphia, Pa.
James Peter Croce.....	New York, N. Y.
Ernest Samuel Cross.....	Baltimore, Md.
John Ewart Culp.....	Ithaca, N. Y.
Morgan Cutts.....	Providence, R. I.
Casimir Joseph Czarnecki.....	Toledo, Ohio
James Harold Danglade.....	Kansas City, Mo.
Donald Howard Daniels.....	Portland, Maine
Harry Anthony Daniels.....	Oklahoma City, Okla.
Charles Francis DeGaris.....	Oklahoma City, Okla.
Harold Archibald Des Brisay.....	Vancouver, B. C., Can.
William Frazier Dobyns.....	Aspinwall, Pa.
Stewart Edward Doolittle.....	Honolulu, T. H.
George B. Dorff.....	Brooklyn, N. Y.

Frederic Griffin Dorwart.....	Muskogee, Okla.
Mark Stovall Dougherty, Jr.....	Atlanta, Ga.
Charles Hilbert Drenckhahn.....	Urbana, Ill.
Charles Dennis Driscoll.....	West Collingswood, N. J.
Lucien Young Dyrenforth.....	Jacksonville, Fla.
Albert Howell Elliot, Jr.....	Santa Barbara, Calif.
Richard Thomas Ellison.....	Philadelphia, Pa.
Richard Donald Evans.....	Los Angeles, Calif.
Constantine P. Faller.....	Harrisburg, Pa.
Harold Fink.....	Brooklyn, N. Y.
Philip Finkle.....	New York, N. Y.
Trenholm Lawrence Fisher.....	Ottawa, Ont., Can.
Greene Smith FitzHugh.....	Boston, Mass.
James Murray Flynn.....	Rochester, N. Y.
Arthur Conwell Fortney.....	Fargo, N. D.
Robert Francis Foster.....	Seattle, Wash.
John Henry Foulger.....	Wilmington, Del.
Harry Joseph Friedman.....	Seattle, Wash.
Mervyn Julius Fuendeling.....	Twin Falls, Idaho
Davis Thayer Gallison.....	Boston, Mass.
Joseph Nicholas Ganim.....	Cincinnati, Ohio
Leon Lloyd Gardner.....	M. C., U. S. Army
Henry Napoleon Gemoets.....	Houston, Tex.
Nicola Gigante.....	Detroit, Mich.
Ralph Lawrence Gilman.....	Storrs, Conn.
Kenneth Franklin Glaze.....	St. Louis, Mo.
Elmer Edward Glenn.....	Springfield, Mo.
Francis Wilcox Gluck.....	Baltimore, Md.
Harold Leon Goldburgh.....	Philadelphia, Pa.
Jacob S. Golden.....	Chicago, Ill.
Grace Arabell Goldsmith.....	New Orleans, La.
Richard Emanuel Gordon.....	New York, N. Y.
William Hyatt Gordon.....	Staten Island, N. Y. (U. S. P. H. S.)
Harold Inman Gosline.....	Ossining, N. Y.
Henry Bragg Gotten.....	Memphis, Tenn.
Barnett Greenhouse.....	New Haven, Conn.
Donald E. Griggs.....	Los Angeles, Calif.
Lewis Perkins Gundry.....	Baltimore, Md.
Alexander B. Gutman.....	New York, N. Y.
Henry Beall Gwynn.....	Washington, D. C.
Byron Ellsworth Hall.....	Rochester, Minn.
Joseph Franklin Hamilton.....	Memphis, Tenn.
Clement Joseph Handron.....	Troy, N. Y.
James Fletcher Hanson.....	Macon, Ga.
William Pickens Harbin, Jr.....	Rome, Ga.
Seale Harris, Jr.....	Birmingham, Ala.
Andrew DeJarnette Hart, Jr.....	University, Va.
Richard Sylvester Hawkes.....	Portland, Maine
Oswald Fenton Hedley.....	Philadelphia, Pa. (U. S. P. H. S.)
Morris Abraham Hershenson.....	Pittsburgh, Pa.
Edward David Hoedemaker.....	Seattle, Wash.
Frank Jackson Holroyd.....	Princeton, W. Va.
Ralph Horton.....	Oneonta, N. Y.
George Hamilton Houck.....	Los Angeles, Calif.

Alson Joye Hull.....	Troy, N. Y.
Maurice Spencer Jacobs.....	Philadelphia, Pa.
Edwin Bosley Jarrett.....	Baltimore, Md.
Sigurd Walter Johnsen.....	Passaic, N. J.
George Johnson.....	Staten Island, N. Y.
Reginald Franklin Jukes.....	Akron, Ohio
Harry Milton Kandel.....	Savannah, Ga.
Jerome George Kaufman.....	Newark, N. J.
Donald Luther Kegaries.....	Rapid City, S. D.
Archibald Donaldson Kennedy.....	Louisville, Ky.
Richard Eugene DeMonbrun Kepner.....	Honolulu, T. H.
Willard Daniel Kline.....	Allentown, Pa.
Albert Preston Knight.....	Sayre, Pa.
Edward Kupka.....	Olive View, Calif.
Michael Lake.....	New York, N. Y.
Wilfred Derwood Langley.....	Sayre, Pa.
Sidney Ferring LeBauer.....	Greensboro, N. C.
Abbe Alzu Ledbetter.....	Houston, Tex.
Thomas Krapfel Lewis.....	Camden, N. J.
John Frank Lieberman.....	M. C., U. S. Army
Noah Stanley Lincoln.....	Mount Morris, N. Y.
John Doyle Littig.....	Kalamazoo, Mich.
Arthur Jones Logie.....	Jacksonville, Fla.
William Lyon Lowrie, Jr.....	Detroit, Mich.
Charles Everard Lyght.....	Northfield, Minn.
John Wilfred MacIntosh.....	Halifax, N. S., Can.
Lucius Emmett Madden.....	Columbia, S. C.
James C. Magee.....	M. C., U. S. Army
Norval Mason Marr.....	St. Petersburg, Fla.
George Graydon Martin.....	Buffalo, N. Y.
John Kay Martin.....	Seattle, Wash.
James Carlin McAdams.....	Fall River, Mass.
Marsh McCall.....	New York, N. Y.
Michael Joseph McInerney.....	Washington, D. C.
Emery James McIntire.....	Carthage, Mo.
Richard Francis McLaughlin.....	Price, Utah
Maud Leonora Menten.....	Pittsburgh, Pa.
John Webster Merritt.....	Jacksonville, Fla.
Hugh McCauley Miller.....	Philadelphia, Pa.
Myron David Miller.....	Columbus, Ohio
William Lindsay Miller.....	Gadsden, Ala.
John Harold Mills.....	Chicago, Ill.
William Rudy Minnich.....	Atlanta, Ga.
Robert Thornhill Monroe.....	Boston, Mass.
Luis Manuel Morales.....	Santurce, P. R.
John Barnhart Morey.....	Ada, Okla.
Carl Grismore Morlock.....	Rochester, Minn.
Gordon Bennett Myers.....	Detroit, Mich.
Walter Cyril Nalty.....	San Fernando, Calif.
Franklin Jesse Nelson.....	Tulsa, Okla.
Harold Gould Newman.....	St. Louis, Mo.
Irwin Louis Vincent Norman.....	M. C., U. S. Navy
Robert Bruce Nye.....	Philadelphia, Pa.

Harry Clifford Oard.....	Jamaica, N. Y.
Richard Ellsworth Olsen.....	Pontiac, Mich.
Alexander Pierce Ormond.....	Akron, Ohio
Dale Pettigrew Osborn.....	Cincinnati, Ohio
Edwin Eugene Osgood.....	Portland, Ore.
Samuel S. Paley.....	New York, N. Y.
Walter Lincoln Palmer.....	Chicago, Ill.
Robert Lawrence Parker.....	Rochester, Minn.
Harold Raymond Peters.....	Baltimore, Md.
John Peters.....	Maywood, Ill.
Manuel de la Pila Iglesias.....	Ponce, P. R.
Thomas Antley Pitts.....	Columbia, S. C.
John Basil Polansky.....	Glenside, Pa.
Herman Marvin Pollard.....	Ann Arbor, Mich.
Perry Franklin Prather.....	Hagerstown, Md.
Homer Edward Prince.....	Houston, Tex.
Meyer S. Rednick.....	Ossining, N. Y.
Ivor Ellsworth Reed.....	Detroit, Mich.
John A. Reisinger.....	Washington, D. C.
Arthur Joseph Revell.....	Pittsburg, Kan.
Cornelius Packard Rhoads.....	New York, N. Y.
Calvus Elton Richards.....	Clifton Springs, N. Y.
Joseph Randall Ridlon.....	Detroit, Mich. (U. S. P. H. S.)
Herbert John Rinkel.....	Kansas City, Mo.
George Porter Robb.....	New York, N. Y.
Milton Edward Rose.....	Decatur, Ill.
Joseph Rosenfeld.....	Youngstown, Ohio
Thomas Llewellyn Ross, Jr.....	Macon, Ga.
Hendrik Marinus Rozendaal.....	Schenectady, N. Y.
Julian Meade Ruffin.....	Durham, N. C.
Emilie Vielt Rundlett.....	Jersey City, N. J.
David Robert Sacks.....	San Antonio, Tex.
David Salkin.....	Hopemont, W. Va.
Russell Lowell Sands.....	Santa Monica, Calif.
Irving Henry Schroth.....	Cincinnati, Ohio
Albert Andrew Schultz.....	Fort Dodge, Iowa
Jacob Schwartz.....	Brooklyn, N. Y.
Roy Wesley Scott.....	Cleveland, Ohio
Thomas Fort Sellers.....	Atlanta, Ga.
Harry Dickey Sewell.....	Huron, S. D.
Thomas Palmer Sharkey.....	Dayton, Ohio
Jesse Bedford Shelmire.....	Dallas, Tex.
Eberle Kost Shelton.....	Los Angeles, Calif.
Noble Pierce Sherwood.....	Lawrence, Kan.
Elbert Henderson Shuller.....	McAlester, Okla.
Harry Willard Shuman.....	Rock Island, Ill.
Stanley T. Simmons.....	Louisville, Ky.
Frank Anthony Simon.....	Louisville, Ky.
Hyman Abraham Slesinger.....	Windber, Pa.
Elliott Plummer Smart.....	Murphys, Calif.
Leslie McKnight Smith.....	El Paso, Tex.
Charles Solomon.....	Brooklyn, N. Y.
Reuben Albert Solomon.....	Indianapolis, Ind.



James Ward Sours.....	Peoria, Ill.
Robert Henry Southcombe.....	Spokane, Wash.
Munro Irving Sparks.....	Cleveland, Ohio
Tom Douglas Spies.....	Cincinnati, Ohio
Charles Henry Sprague.....	Boise, Idaho
Thomas Austin Starkey.....	Beardstown, Ill.
Henry Barthell Steinbach.....	Detroit, Mich.
Gilbert Miller Stevenson.....	Gamboa, Canal Zone
James Graves Stewart.....	Topeka, Kan.
Merritt Henry Stiles.....	Philadelphia, Pa.
Eugene Solomon Talbot.....	Chicago, Ill.
David Tenner.....	Baltimore, Md.
Chester Quay Thompson.....	Omaha, Nebr.
George C. Thosteson.....	Detroit, Mich.
John Walter Torbett, Jr.....	Marlin, Tex.
James Harvey Townsend.....	Boston, Mass.
Frederick Erwin Tracy.....	Middletown, Conn.
William Hugh Trimble.....	Atlanta, Ga.
Woodford Bates Troutman.....	Louisville, Ky.
Pat Alexander Tuckwiller.....	Charleston, W. Va.
David Ulmar.....	New York, N. Y.
Lee Douglas van Antwerp.....	Meriden, Conn.
Stuart L. Vaughan.....	Buffalo, N. Y.
Edmond Michael Walsh.....	Omaha, Nebr.
Preston Hepburn Watters.....	Rochester, N. Y.
Harold Emanuel Waxman.....	Pittsburgh, Pa.
Joseph Treloar Wearn.....	Cleveland, Ohio
George William Weber.....	Albany, N. Y.
Albert Weinstein.....	Nashville, Tenn.
Joseph Weinstein.....	Brooklyn, N. Y.
Robert Lomax Wells.....	Washington, D. C.
George Arthur Westfall.....	Halstead, Kan.
Samuel Whitehouse.....	Baltimore, Md.
Frederick Rendell Whittlesey.....	Morgantown, W. Va.
John Harrington Willard.....	Philadelphia, Pa.
Frank Wiley Wilson.....	M. C., U. S. Army
George Campbell Wilson.....	Wallingford, Conn.
Walter LaFollette Winkenwerder.....	Baltimore, Md.
Malcolm Duncan Winter.....	Miles City, Mont.
Stanley George Wolfe.....	Shreveport, La.
Jonathan Knight Williams Wood.....	Troy, Pa.
Burbridge Scott Yancey.....	Harrisonburg, Va.
Richard Hale Young.....	Evanston, Ill.
Michael Zeller.....	Chicago, Ill.
Edwin Eugene Ziegler.....	Boston, Mass. (U. S. P. H. S.)
Salvador Zubiran.....	Mexico City, D. F.

## ELECTIONS TO ASSOCIATESHIP, MARCH 31, 1940

John Delbert Adcock.....	Ann Arbor, Mich.
James Moses Alexander.....	Charlotte, N. C.
Luis Antonio Amill.....	New York, N. Y.
Charles Lee Anderson.....	Jackson Heights, N. Y.

James Fleming Anderson.....	Los Angeles, Calif.
John Edmund Ashby.....	Dallas, Tex.
Richard Bardon.....	Duluth, Minn.
George Newton Barry.....	Oklahoma City, Okla.
Reuben Berman.....	Minneapolis, Minn.
Arthur Bernstein.....	Newark, N. J.
Philip George Crosbie Bishop.....	New York, N. Y.
Belford Christy Blaine.....	Pottsville, Pa.
Leon L. Blum.....	Terre Haute, Ind.
Wayne G. Brandstadt.....	U. S. Army
Kenneth Arthur Brewer.....	U. S. Army
Omar Jesse Brown.....	U. S. Navy
Harold J. Brumm.....	Rochester, Minn.
Bert Montell Bullington.....	Ann Arbor, Mich.
Eugene Paul Campbell.....	Philadelphia, Pa.
Lawrence Sherwood Carey.....	Philadelphia, Pa.
Harry Dumont Clark.....	Denver, Colo.
James Harwood Closson.....	Philadelphia, Pa.
Sumner S. Cohen.....	Oak Terrace, Minn.
Aloysius John Berchmans Connolly.....	Washington, D. C.
Darrell Clayton Crain, Jr.....	Washington, D. C.
Joseph David Croft.....	Evanston, Ill.
Lester A. Crowell, Jr.....	Lincolnton, N. C.
Alexander George Davidson.....	Brooklyn, N. Y.
Albert Murray DeArmond.....	Indianapolis, Ind.
Paul Mason de la Vergne.....	Meriden, Conn.
Karl LaVon Dickens.....	New Orleans, La.
Paul Dufault.....	Rutland, Mass.
William Miller Dugan.....	Indianapolis, Ind.
Herman Franklin Easom.....	Sanatorium, N. C.
Hamblen Cowley Eaton.....	Harrisburg, Pa.
Francis Busha Edmundson.....	Pittsburgh, Pa.
Reginald Campbell Edson.....	Hopemont, W. Va.
Eugene Eisner.....	Osawatomie, Kan.
Clarence Kilgore Elliott.....	Lincoln, Nebr.
Frederick George Elliott.....	Edmonton, Alta.
Lowell Ashton Erf.....	Berkeley, Calif.
Caryl Ray Ferris.....	Kansas City, Mo.
Milton Bayard Filberbaum.....	Brooklyn, N. Y.
Meyer Herbert Fineberg.....	Cleveland, Ohio
Dan William Fisher.....	Lansing, Mich.
Paul Donald Foster.....	Los Angeles, Calif.
Leon Jacob Galinsky.....	Oakdale, Iowa
Curtis Ferbert Garvin.....	Cleveland, Ohio
James Thomas Gilbert, Jr.....	Bowling Green, Ky.
Hugh Richmond Gilmore, Jr.....	U. S. Army
Herman Coddington Graves.....	Grand Junction, Colo.
Frank John Gregg.....	Pittsburgh, Pa.
Frank William Halpin.....	Fort Worth, Tex.
Charles Edward Hamilton.....	Lafayette, La.
Meyer Max Harrison.....	Louisville, Ky.
Thomas Haynes Harvill.....	Ann Arbor, Mich.
Theodore Henry Harwood.....	Burlington, Vt.

Paul Hayes.....	U. S. Army
Edward McGowan Hedgpeth.....	Chapel Hill, N. C.
Standiford Helm.....	Evanston, Ill.
Roger Andrew Hemphill.....	Oneonta, N. Y.
Edward Herbert, Jr.....	New York, N. Y.
Federico Hernandez-Morales.....	San Juan, P. R.
Herman S. Hoffman.....	Washington, D. C.
Jesse Morris Horn.....	Fort Worth, Tex.
Elbridge Eugene Johnston.....	St. Johnsbury, Vt.
John Kenneth Karr.....	Milwaukee, Wis.
Thomas Francis Keliher.....	Washington, D. C.
William Karl Keller.....	Louisville, Ky.
Henry Samuel Kieser.....	Reading, Pa.
Jacob Joseph Kirshner.....	Philadelphia, Pa.
Morris Kleinbart.....	Philadelphia, Pa.
Alva Allen Knight.....	Chicago, Ill.
Clarence Lunsford Laws.....	Atlanta, Ga.
Edwin Delano Lee.....	Exeter, N. H.
Charles Lurn Leedham.....	U. S. Army
John Boyer Levan.....	Reading, Pa.
Howard Avery Lindberg.....	Chicago, Ill.
Eugene John Lippschutz.....	Buffalo, N. Y.
Emmett Bryan Litteral.....	U. S. Army
Angelo Luigi Luchi.....	Wilkes-Barre, Pa.
Frank Luciano.....	Richmond Hill, N. Y.
Robert Edward Lyons, Jr.....	Bloomington, Ind.
George Carlyle Mackie.....	Wake Forest, N. C.
Perry Scott MacNeal.....	Ann Arbor, Mich.
William Robert Manlove.....	U. S. Navy
Benjamin Markowitz.....	Bloomington, Ill.
George Elmer Martin.....	Pittsburgh, Pa.
Louis Everett Martin.....	Los Angeles, Calif.
Neely Cornelius Mashburn.....	U. S. Army
Joseph Ralph Mayer.....	Rochester, N. Y.
Merton Melrose Minter.....	San Antonio, Tex.
Roger Sherman Mitchell, Jr.....	Glens Falls, N. Y.
John Russell Egbert Morgan.....	Toronto, Ont.
Mark Tad Morgan.....	U. S. Army
Isidor Mufson.....	New York, N. Y.
Allison Lee Ormond.....	Black Mountain, N. C.
George Colville Owen.....	Oshkosh, Wis.
Robert Collier Page.....	New York, N. Y.
Victor Louis Pellicano.....	Buffalo, N. Y.
Abraham Penner.....	New York, N. Y.
Evans William Pernokis.....	Chicago, Ill.
Frank Hart Peters.....	New York, N. Y.
Kenneth Elwood Quickel.....	Harrisburg, Pa.
William Frederick Rexer.....	Brooklyn, N. Y.
Ella Roberts.....	Philadelphia, Pa.
Albert Henry Robinson.....	U. S. Army
William Dodd Robinson.....	Ann Arbor, Mich.
Harry Plummer Ross.....	Richmond, Ind.
James W. H. Rouse.....	San Antonio, Texas

John Griswold Ruth.....	Ann Arbor, Mich.
David Ivan Rutledge.....	Rochester, Minn.
Milton Samuel Sacks.....	Baltimore, Md.
John Philip Sampson.....	Santa Monica, Calif.
James Joseph Saperio.....	U. S. Navy
Frederick Theodore Schnatz.....	Buffalo, N. Y.
Jacob Wolfe Schoolnic.....	East Liverpool, Ohio
Henry Alfred Schroeder.....	New York, N. Y.
Leon Schwartz.....	Philadelphia, Pa.
John Bernard Schwedel.....	New York, N. Y.
Edward George Seybold.....	Ann Arbor, Mich.
Emory Lee Shiflett.....	Louisville, Ky.
William Merrill Silliphant.....	U. S. Navy
James Francis Slowey.....	Cleveland, Ohio
Frank Edward Smitli, Jr.....	New York, N. Y.
Leonard Gerard Steuer.....	Cleveland, Ohio
Russell Alvin Stevens.....	Wilkes-Barre, Pa.
Rendall Risley Strawbridge.....	Philadelphia, Pa.
Christopher James Stringer.....	Lansing, Mich.
Leonard Neil Swanson.....	U. S. Army
Frederick Charles Swartz.....	Rochester, Minn.
Verne Wilson Swigert.....	Evanston, Ill.
James Sherwood Taylor.....	U. S. Army
Rufus Henry Temple.....	Kinston, N. C.
Joseph Lawn Thompson, Jr.....	Washington, D. C.
William Albert Thornhill, Jr.....	Charleston, W. Va.
Richard Nelson Tillman.....	Ann Arbor, Mich.
Robert Lane Ware.....	U. S. Navy
Hugh Joseph Joachin Welch.....	Washington, D. C.
Oliver William Welch.....	Fairfield, Ala.
Charles Grant Williamson.....	Brooklyn, N. Y.
Olin Glenwood Wilson.....	Canton, Ohio
Zolton Tillson Wirtschafter.....	Cleveland, Ohio
Raymond Joseph Wyrens.....	Omaha, Nebr.

#### NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. Walter E. Vest, Huntington, W. Va.  
 Dr. Chester W. Waggoner, Toledo, Ohio

#### GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged:

##### *Books*

Dr. Henry Joachim, F.A.C.P., Brooklyn, N. Y., "Practical Bedside Diagnosis and Treatment."  
 Dr. Luis Manuel Morales, F.A.C.P., Santurce, P. R., "Dirigiendo Al Niño."

*Reprints*

Dr. Anthony C. Cipollaro, F.A.C.P., New York, N. Y.—2 reprints;  
Dr. Lucien Y. Dyrenforth, F.A.C.P., Jacksonville, Fla.—1 reprint;  
Dr. Julius Friedenwald, F.A.C.P., Baltimore, Md.—1 reprint;  
Dr. Donald W. Ingham (Associate), Washington, D. C.—6 reprints;  
Dr. John L. Kantor, F.A.C.P., New York, N. Y.—20 reprints;  
Dr. Wilbur F. Keller, F.A.C.P., Oklahoma City, Okla.—2 reprints;  
Dr. Manfred Kraemer, F.A.C.P., Newark, N. J.—2 reprints;  
Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa.—3 reprints;  
Dr. John H. Musser, F.A.C.P., New Orleans, La.—29 reprints;  
Dr. H. M. Read (Associate), York, Pa.—1 reprint;  
Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio—3 reprints;  
Dr. Rufus A. Schneiders (Associate), San Diego, Calif.—4 reprints;  
Dr. Bernard M. Scholder (Associate), Mt. Vernon, N. Y.—1 reprint;  
Dr. James Ralph Scott, F.A.C.P., New York, N. Y.—2 reprints;  
Dr. Charles H. Sprague, F.A.C.P., Boise, Idaho—1 reprint;  
Dr. James L. Wade (Associate), Parkersburg, W. Va.—4 reprints.

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Dr. David Riesman, F.A.C.P., was re-elected president and Dr. Thomas M. McMillan, F.A.C.P., was re-elected vice president of the Philadelphia Heart Association at the 18th annual meeting of this society. Dr. Francis C. Wood, F.A.C.P., was named secretary and elected to the board of directors. Among the others elected to the board of directors were Dr. Mary H. Easby, F.A.C.P., Dr. Louis B. Laplace, F.A.C.P., and Dr. Joseph B. Vander Veer (Associate).

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Dr. Ralph H. Boots, F.A.C.P., New York, N. Y., has been appointed Assistant Clinical Professor of Medicine at Columbia University College of Physicians and Surgeons.

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Dr. Ross M. Lymburner, F.A.C.P., Hamilton, Ont., was the guest speaker at the meeting of the Sault Ste. Marie Medical Society, at Sault Ste. Marie, Ont., March 9. The subject of the address was "Heart Disease in General Practice."

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Dr. Hyman I. Goldstein (Associate), Camden, N. J., has been appointed Editor in charge of the Section on Historical Gastro-enterology of the Review of Gastro-enterology.

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Dr. R. W. Bradshaw, F.A.C.P., Head of the Oberlin College Student Health Service and Director of Allen Hospital, addressed the American Association of School Administrators at St. Louis, February 25, on "Eye Health of College Students," and spoke on the same subject at a dinner meeting of the Hygiene Club of Kent State University, Kent, Ohio, February 29. Dr. Bradshaw is chairman of the Eye Health Committee of the American Student Health Association and past-president of this organization.

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Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., addressed a meeting of the International Association of Dental Research in Philadelphia, Pa., recently on "A Study of the General Predisposing Factors of Parodontal Disease."

Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn., was recently appointed Full Attending Physician in Metabolism at the Grace Hospital in New Haven.

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The Fifth Annual Postgraduate Institute of the Philadelphia County Medical Society was held in Philadelphia April 15-20, 1940, under the presidency of Dr. Rufus S. Reeves, F.A.C.P. Dr. Edward L. Bortz, F.A.C.P., is President-Elect of the Society.

The program of this meeting emphasized the clinical features of Cardiology, Vascular and Nephritic Diseases. Papers were presented by thirty-two members of the American College of Physicians.

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The Northern Medical Association of Philadelphia recently held its 93rd Annual Testimonial Dinner to all living ex-presidents of the Association. Among the members of the College who were honored at this dinner were: Dr. David Riesman, F.A.C.P., Dr. A. C. Morgan, F.A.C.P., Dr. Mitchell Bernstein, F.A.C.P., Dr. Jacob Cahan, F.A.C.P., all of Philadelphia, Pa., and Dr. Hyman I. Goldstein (Associate), Camden, N. J.

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Dr. Edward B. Krumbhaar, F.A.C.P., Philadelphia, Pa., was recently elected President of the College of Physicians of Philadelphia.

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Dr. Robert S. Berghoff, F.A.C.P., Clinical Professor of Medicine at Loyola University School of Medicine, and Chairman of the Scientific Service Committee of the Illinois State Medical Society, has been elected to membership in the Alpha Omega Alpha Honorary Medical Society in the chapter of his alma mater, St. Louis University. He was inducted at St. Louis on April 24 and on that occasion was the principal speaker. The subject of his address was "Senile Ecstasy."

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Dr. John H. Musser, F.A.C.P., New Orleans, La., was awarded the Alumni Award of Merit of the University of Pennsylvania School of Medicine on Founder's Day, January 17, in connection with the bicentennial of the university.

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Dr. Fred N. Miller (Associate), Eugene, Ore., was elected vice president of the American Student Health Association at its recent annual meeting in New York.

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Dr. Nathan Einhorn, F.A.C.P., Philadelphia, Pa., has been named chief and Dr. Leonard G. Rowntree, F.A.C.P., Philadelphia, Pa., has been named consultant of the new department of endocrinology recently opened by the Jewish Hospital.

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Dr. Joseph P. Brennan, F.A.C.P., Pendleton, Ore., was recently named president of the Umatilla County Medical Society, which was reorganized during February.

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Dr. George Morris Piersol, F.A.C.P., Philadelphia, Pa., was recently named a member of the advisory board of the state department of health by Governor Arthur H. James.

Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass., Dr. James A. Lyon, F.A.C.P., Washington, D. C., and Dr. Allen K. Krause, F.A.C.P., Baltimore, Md., were recently elected to membership in the Medical Council, Veterans' Administration.

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Dr. Virgil P. W. Sydenstricker, F.A.C.P., Augusta, Ga., has been awarded a grant of \$6,000 by the Markle Foundation to continue his studies on pellagra. Dr. Sydenstricker is a professor of medicine at the University of Georgia School of Medicine.

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Dr. Leonard G. Rowntree, F.A.C.P., Philadelphia, Pa., delivered the Roger Morris Memorial Lecture for 1940 at the University of Cincinnati College of Medicine on March 25. The subject of his address was "The Suprarenal Gland and Its Diseases."

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Dr. George R. Herrmann, F.A.C.P., Galveston, Texas, was elected secretary of the Texas Club of Internal Medicine at the annual meeting in Dallas in February.

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Dr. Thomas N. Spessard (Associate), Norfolk, Va., was elected president of the Neuropsychiatric Society of Virginia at the annual meeting in Richmond, February 7.

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#### EIGHTH AMERICAN SCIENTIFIC CONGRESS

The Eighth American Scientific Congress will be held in Washington, D. C., from May 10 to 18, 1940, under the auspices of the Government of the United States. An invitation on behalf of the President has been extended to the Governments of the American Republics members of the Pan American Union to participate in the forthcoming meeting, which is held in connection with the celebration of the fiftieth anniversary of the founding of the Pan American Union.

The Congress will be divided into eleven sections covering the fields of the various sciences, law and education.

Section V will be devoted to Public Health and Medicine. The program of this section will include sessions devoted to the following topics: education in public health and medicine; nutrition; tuberculosis; chemotherapy; heart disease; cancer; tropical and other diseases of current interest.

There will be arranged a visit to the National Institute of Health with opportunity to observe current investigations in many fields.

The Surgeon General has expressed the hope that there will be a large attendance at the Congress from the members of the American College of Physicians.

## OBITUARIES

### DR. AUSTEN FOX RIGGS

Dr. Austen Fox Riggs died in Stockbridge, Massachusetts, on March 5, 1940. Dr. Riggs graduated from Harvard with the degree of A.B. in 1898. He obtained his medical degree in 1902 from the College of Physicians and Surgeons of Columbia University and then served for two years as interne in medicine in the Presbyterian Hospital, New York.

In 1904 he became associated with Professor Walter B. James in the practice of general medicine but in 1907 he developed pulmonary tuberculosis. It demonstrates the calibre of the man that he converted this tragic interruption of a brilliant medical career into a stepping stone by which he later achieved eminence in his later chosen specialty of neuropsychiatry.

Advised that a city career was undesirable he retired to the country at Stockbridge and there built up his health and at the same time a private practice in the treatment of functional nervous disorders and also became one of the leading citizens of that charming New England village.

His extraordinary and hitherto unrecognized qualifications for this type of medical practice soon brought to him both success and professional reputation and by 1919 he had gathered support for the fulfillment of his dream to establish an institution which would serve to widen the scope of his activities and particularly to make available to patients of moderate means the advantages of the system of treatment and reëducation which he had developed. So in that year, The Austen Riggs Foundation was established at Stockbridge, with Dr. Riggs as its Founder and Medical Director.

This institution, quite unique in its character, has continued under his direction ever since with increasing prestige and usefulness, not only to the large number of patients who there have sought help, but also to the medical profession. Stockbridge became a center for postgraduate education in this branch of medicine and many are the physicians who during these years have been thoroughly trained there or have been to some degree affected by its influence. This Foundation is a monument not only to Dr. Riggs' rare professional attainments but also to his executive ability and his unusual qualities of leadership.

That Dr. Riggs' capacities could not be confined to a small village and were recognized and deeply appreciated by the outside profession is evidenced by the fact that since 1919 and up to the time of his death he was Consulting Psychiatrist to the Sharan Connecticut Hospital, to the House of Mercy, Pittsfield, Massachusetts, to the Indian Mountain School, Lakeville, Connecticut, to Vassar College where he was also Lecturer and to Williams College.

Since 1922 he has been Clinical Professor of Neurology in the College of Physicians and Surgeons of Columbia University.



In 1937 the honorary degree of Sc.D. was conferred upon him by Williams College.

He was a member of many Boards and Medical Societies, among them The American College of Physicians, The American Board of Psychiatry and Neurology, The American Psychiatric Association, The New York Academy of Medicine, The National Committee of Mental Hygiene and the Massachusetts Society for Mental Hygiene of which he was a member of the Board of Directors.

He was the author of several books and also of numerous articles in medical periodicals dealing with his specialty.

Dr. Riggs has made a great contribution to American medicine. His chosen field is a very difficult one. He cultivated it with a saneness and common sense for which not all workers in this branch of medicine are notable. A thorough student, he was conversant with all the various theories and practices of others, but he possessed the judgment to discard the unsound and to avoid the fads and fancies.

He developed a system quite his own, logical, understandable, and practically successful, which will leave a permanent impress upon the practice of psychiatry, and hundreds of his patients rise and call him blessed for what he has done for them.

Dr. Riggs' record of achievement would have been impossible had it not been for his unusual personality. He was dynamic but sympathetic; forceful but understanding. Appreciative as he was of the innumerable motivations of human behavior he was resourceful in unravelling the tangled skeins and in weaving a new pattern for the conduct of life. He possessed a rare personal charm which added affection to the respect which his patients had for him. This gave him great power which he exercised with restraint and circumspection.

In his family and in his wide circle of devoted friends he was loved to an extent beyond the reach of ordinary men.

He was a rare person. His going has left a gap which cannot be filled.

JAMES ALEXANDER MILLER

#### DR. JAMES CARPINTER COBEY

Dr. James Carpinter Cobey, aged 65, died suddenly in Los Angeles, California on January 29, 1940 of coronary thrombosis.

He was born in Charles County, Maryland, November 4, 1874. His early education was in the public schools and at Durham Academy. His medical training was obtained at the College of Physicians and Surgeons in Baltimore, Maryland. Following graduation he spent some months on the staff at the Hospital for the Insane at Catsonville, Maryland. He came to Frostburg in the fall of 1896 and devoted his time to the practice of medicine and surgery.

Dr. Cobey was a member and former president of the Alleghany-Garrett County Medical Society. He was also a member of the Medico-Chirurgical Faculty of Maryland and of the American Medical Association and an Associate of the American College of Physicians. He was a member of the staff of the Miners Hospital, Frostburg.

During the World War, Dr. Cobey served in the medical corps first at Fort Oglethorpe and later at the Staten Island Hospital resigning his commission as captain in May of 1919. He remained a member of the Medical Reserve Corps.

His fraternal affiliations included the Elks and the Knights of Pythias. He was a member of the board of Directors of Frostburg National Bank and was a life long member of St. John's Episcopal church and for many years served as a vestryman.

Dr. Cobey and his family were always active and leaders in civic activities and gave large contributions to all charitable organizations and undertakings. He enjoyed a very large practice in this community.

Funeral services were held in Frostburg on February 3, 1940 with burial in the Arlington National Cemetery on February 5, 1940. He will be greatly missed by his patients and his many friends in the profession.

W. O. McLANE

#### DR. WALTER W. BOARDMAN

On February 11, 1940, Dr. Boardman succumbed to a long, chronic illness that had confined him to bed for several weeks before the end came. Walter Whitney Boardman was born December 9, 1883, in Oakland, California. He graduated from the University of California at Berkeley, California, in 1906, entering Cooper Medical College in San Francisco the same year, and obtaining his medical degree at this institution in 1909. Following graduation he served as an interne in the Lane Hospital, part of Cooper Medical School. During the years 1910 to 1912 he was an assistant in Roentgenology and House Officer at the Johns Hopkins Hospital. In 1912 on returning to San Francisco, Dr. Boardman was appointed to the staff of the Stanford University Medical School in charge of the Department of Roentgenology. During the next few years he worked faithfully in this field, but during the World War enlisted in the Navy as a First Lieutenant. On his return to San Francisco at the close of the War he accepted a clinical appointment in Internal Medicine at Stanford University Medical School, becoming interested in the field of gastro-enterology. In 1925 he became an Associate Clinical Professor of Medicine and later was advanced to Clinical Professor. In 1928 Dr. Boardman became a "Fellow" of the College and later became a diplomate of the American Board of Internal Medicine.

He was a member of the San Francisco County Medical Society, the California State Medical Society and the American Medical Association. He had served as Vice-President and President of the California Academy of

Medicine, was a member of the Pacific Coast Interurban Society and the American Gastro-Enterological Association.

His contributions to leading medical journals were numerous and of distinct merit. As an Internist and Consultant, Dr. Boardman stood high in this community, but his ability and zeal were only a portion of his successful attributes, for he had a kindly personality and friendly quality that inspired patients and associates and made lasting friends. His death came at a time when he was at the height of his career and when his help and advice in his County Medical Society were often requested and much prized.

ERNEST H. FALCONER, M.D., F.A.C.P.

Governor for Northern California

### DR. JOSHUA M. VAN COTT

Dr. Joshua Marsden Van Cott was born in Brooklyn, N. Y., June 12, 1861, and died February 8, 1940.

Dr. Van Cott received his degree of Doctor of Medicine from the Long Island College Hospital Medical School in 1885. In 1887 he became Pathologist at the Long Island College Hospital and was retained in that capacity until 1924. He also taught Pathology, Bacteriology and Clinical Medicine there until 1917. He had been a Pathology student at the Koch Laboratories in Berlin, Germany, and continued his work in that field through his association with the Long Island College Hospital, where, in 1914, he became Professor Emeritus of Pathology and Clinical Medicine at the Medical School. He was also a Trustee of the Hospital. In connection with his work in Pathology he returned to Berlin in 1891 to obtain for use in this country the tuberculin serum discovered by Dr. Robert Koch.

Dr. Van Cott had been President of the Professional Staff of the Brooklyn Hospital since 1930 and was President of the Board of Trustees of the Hoagland Laboratories attached to the Long Island College Hospital. He became an Attending Physician at the Brooklyn Hospital in 1910, Chief Attending Physician seven years later, and Senior Physician in 1925. He was also a Consulting Physician at the Kings County, St. John's, Wyckoff Heights and the Methodist Hospitals. He was Chairman of Public Health and Education of the New York State Medical Society, 1912-1924 and Vice-President of the same Society, 1927-1928. He had been President of the Kings County Medical Society in 1909, and in 1913 served on the Advisory Committee of the New York Board of Health. He was a founder of the Associated Physicians of Long Island, Member of the New York Academy of Medicine, the New York Pathological Society, the American Medical Association, and had been a Fellow of the American College of Physicians since 1916. He leaves a widow, the former Miss Evelyn Shattuck.

CHARLES F. TENNEY, M.D., F.A.C.P.,

Governor for Eastern New York

# ANNALS OF INTERNAL MEDICINE

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## THE EFFECT OF SPECIFIC AGENTS EXTRACTED FROM SOIL MICROORGANISMS UPON EXPERIMENTAL BACTERIAL INFECTIONS \*

By RENÉ J. DUBOS, *New York, N. Y.*

ORGANIC matter does not accumulate in nature; it rapidly becomes the prey of countless species of microorganisms which break it down, stepwise, to carbon dioxide, water, ammonia, and mineral salts. It is known moreover that, under natural conditions, each one of these microbial species is adapted to the performance of a limited, well-defined biochemical task. It seems certain, therefore, that one can find in nature microorganisms selectively adapted to the decomposition of almost every conceivable type of organic compound.<sup>9</sup>

Like all living cells, microorganisms carry out their biochemical function through the agency of enzymes and other catalysts. In many cases these catalysts can be extracted in an active form from the microbial cells which produce them, and they are often found to exhibit a remarkable specificity with reference to the type of reaction which they can bring about. Because of their cellular origin, microbial catalysts are able to operate under physiological conditions (pH, temperature, etc.) and this property together with their specificity, renders them ideal reagents for the analysis of biological problems. It is apparent, therefore, that one can select from microbial life a great variety of specific, physiological reagents, which should find many applications in the problems of medicine.<sup>9, 10</sup>

During the past few years, this point of view has found its application in the isolation from soil of new bacterial species, which produce specific catalysts selectively adapted to the study of some biochemical and immunological problems.<sup>9, 10, 14, 15, 25</sup> The present report deals with two types of reagents which were extracted from various species of soil bacteria and which, by entirely different mechanisms, protect experimental animals against certain bacterial infections.

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\* Read at the Cleveland meeting of the American College of Physicians, April 4, 1940.  
From The Hospital of The Rockefeller Institute for Medical Research.

*Bacterial Enzymes Which Decompose the Capsular Polysaccharides of Virulent Pneumococci.* It is well known that the capsular polysaccharides of encapsulated pneumococci determine the serological specificity and condition the virulence of these organisms. The specific antibodies present in the sera of animals immunized with encapsulated pneumococci of the different types, afford protection against pneumococcus infections because of their ability to react with the polysaccharides which constitute the bacterial capsules.<sup>1, 2, 20</sup> It will be shown in the following discussion that enzymes capable of decomposing the capsular substances of pneumococci can also protect experimental animals against infection with these organisms.

As far as is known, the capsular polysaccharides of pneumococci are not decomposed by enzymes of animal or plant origin, nor are they attacked by common species of bacteria, actinomyces or molds. It was possible, however, to isolate from soil a new bacterial species, a sporulating bacillus, which hydrolyzes the specific polysaccharide of Type III pneumococcus.<sup>11</sup> From cultures of this soil bacillus, one can extract a soluble enzyme which hydrolyzes this specific carbohydrate<sup>5, 11, 12</sup> and which robs it at the same time of its serological activity; the enzyme is extraordinarily specific in its action against the polysaccharide of pneumococci of Type III and in particular has been found inactive against all the other bacterial polysaccharides so far tested.<sup>4</sup>

The addition of active enzyme to nutrient media does not inhibit the growth or cause the lysis of pneumococci; however, pneumococci of Type III, when cultivated in media containing the specific enzyme, appear deprived of their capsules and fail to agglutinate in specific antiserum of the homologous type. That the *function* of elaborating the type-specific substance is not destroyed by the enzyme, however, is shown by the fact that pneumococci so treated continue to produce the capsular polysaccharide, when transferred to a medium devoid of the active hydrolyzing agent. These two facts, namely, the decomposition of the isolated specific carbohydrate and the destruction of the capsule, without interference with the essential metabolic functions of the pneumococcus cells, indicate that the active principle is directed against this single, specific substance—the capsular polysaccharide—and not against the cell as a whole.<sup>11</sup>

Enzymes capable of attacking the capsular polysaccharides of other pneumococcus types have now been obtained from different strains of soil bacteria.<sup>25, 26, 27, 28, 29</sup> Several of these enzymes exhibit a remarkable specificity and can even differentiate between polysaccharides which give cross-reactions in immune antisera. For instance, the polysaccharide of gum acacia which reacts in Type III pneumococcus antiserum is not affected by the enzyme which hydrolyzes the Type III polysaccharide.<sup>11</sup> Even more striking is the difference between the two enzymes attacking the polysaccharides of Type III and Type VIII pneumococcus. Both these substances are composed of glucose and glucuronic acid in different ratios, and because of this chemical

relationship, they exhibit a certain amount of cross reaction in immune sera.<sup>17, 21</sup> On the contrary, the bacterial enzymes developed against each one of the polysaccharides fail to attack the other<sup>30</sup>; in other words, the enzymes are even more specific than are the antibodies obtained by immunization of experimental animals with the capsular antigens of pneumococci.

Not only are the bacterial polysaccharidases capable of decomposing the capsular substances in vitro, but they also exhibit the same activity in vivo.<sup>3</sup> In fact, they can protect experimental animals against infection with virulent pneumococci. In view of the specificity which the enzymes exhibit in vitro, it was to be expected that the protection induced in experimental animals would exhibit a specificity determined by the chemical nature of the polysaccharide of the particular pneumococcus type used for infection.<sup>3, 18, 19</sup> It is shown in table 1 for instance, that the enzyme which decomposes the Type

TABLE I  
Specificity of the Protective Action of Type III Enzyme  
(Reprinted from the Journal of Experimental Medicine)

Infecting dose of Pneumococcus	Enzyme (Lot 4-α) 0.5 c.c.			No enzyme		
	Pneumococcus Type I	Pneumococcus Type II	Pneumococcus Type III	Virulence controls		
				Type I	Type II	Type III
c.c.						
0.1	—	—	S	—	—	—
0.01	—	—	S	—	—	—
0.001	—	—	S	—	—	—
0.0001	D20	D34	S	—	—	—
0.00001	D24	D34	S	D22	D36	D34
0.000001	D34	D34	S	D34	D36	D34
0.0000001	—	—	—	D34	D20	D72

S = survived.

D = Death of animal; the numeral indicates the number of hours before death, or the time at which the animal was found dead.

— = Not done.

III capsular substance can protect mice against infection with 1,000,000 fatal doses of pneumococci of this type, but is entirely ineffective against pneumococci of Types I and II. The same enzyme exhibits also a curative effect on the dermal infection of rabbits caused by Type III pneumococci.<sup>18, 19</sup> Following the injection of the enzyme in suitable amounts into infected rabbits, the blood stream becomes free of bacteria, the focal area of infection becomes sterilized and the disease process ceases. The enzyme also exerts a favorable influence upon experimental pneumonia produced in monkeys of the *M. cynomologos* species with Type III pneumococci. Treatment was followed by cessation of spread of the pneumonic lesion, sterilization of the blood, and early recovery except in animals in which the severity of the dis-

ease was extreme. Whereas in the untreated animals a high incidence of empyema and pericarditis was observed, suppurative complications were apparently prevented by adequate enzyme therapy.<sup>16</sup>

The mechanism of the protection so induced has been revealed by a study of the peritoneal exudate of mice during the course of infection with Type III pneumococci.<sup>3</sup> As could be expected, the peritoneal exudate of the untreated mice showed numerous encapsulated pneumococci free in the fluid and the number of encapsulated bacteria increased as the infection progressed. In contrast to this, the pneumococci in the enzyme-treated animals were already found to be devoid of capsules two hours after treatment. At the end of four hours, the treated animals showed only a few decapsulated cells outside of the leukocytes although many bacteria were present in the phagocytic cells. It is obvious, therefore, that the protective action of the enzyme lies in its capacity to decompose the capsular substance of the infectious agent, and thus to render the latter susceptible to phagocytosis (figures 1, 2, 3, 4).

An understanding of this mechanism makes clear the therapeutic limitations of the enzyme. This reagent only initiates a process which has to be completed by the phagocytic cells of the infected host. When, however, the disease process is of extreme severity and the entire cellular mechanism of the body is markedly depressed, the animal may no longer possess the capacity to dispose of the organisms rendered vulnerable by the specific action of the enzyme.

*A Selective Bactericidal Agent Extracted from Cultures of a Sporulating Bacillus.* As stated in the introduction, one can discover in nature microorganisms capable of decomposing almost every conceivable type of organic substance. It appeared possible that there also exist microorganisms capable of attacking not only soluble, isolated compounds, but even the intact liv-

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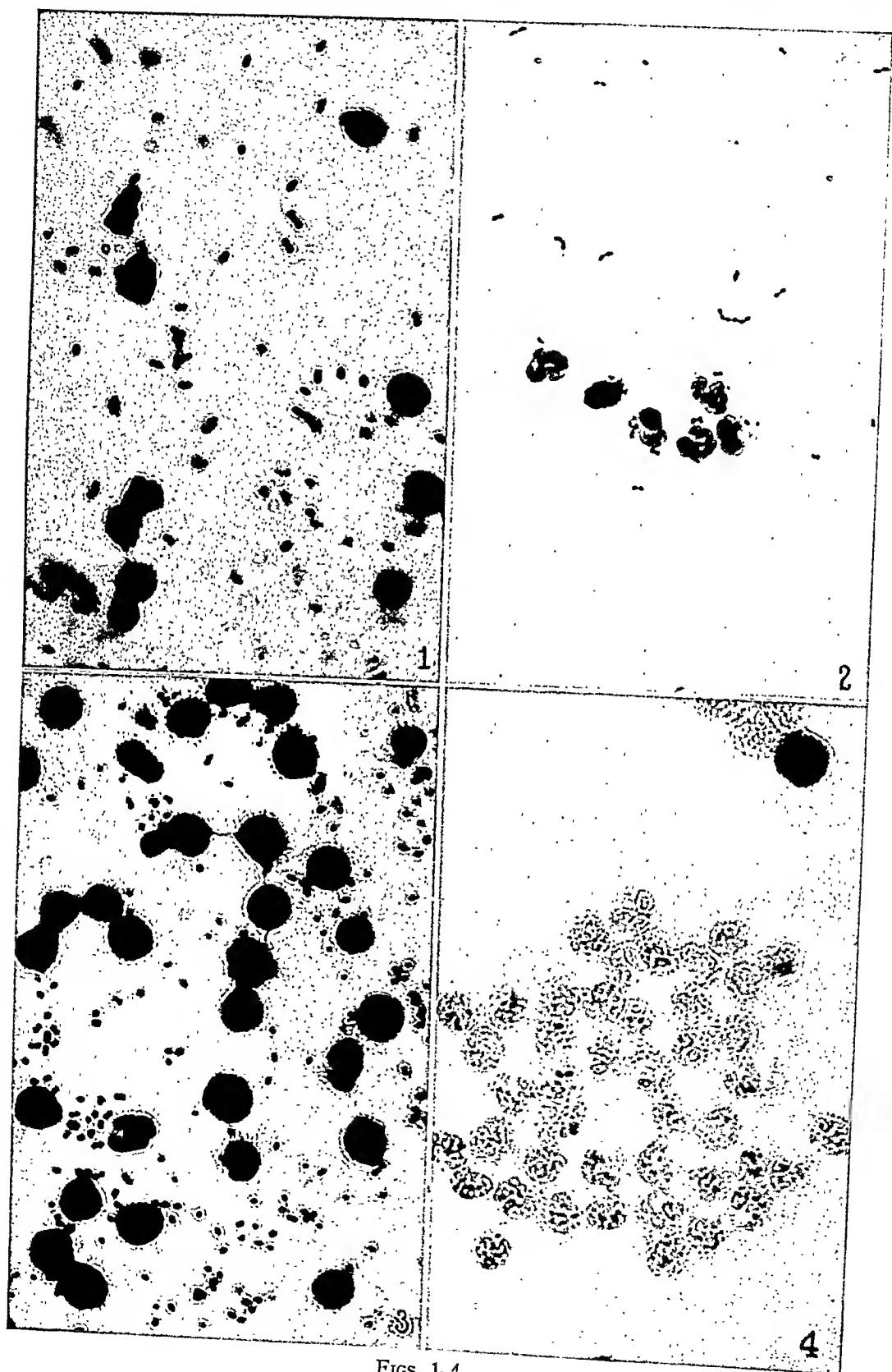
FIG. 1. Photomicrograph of a stained preparation of the peritoneal exudate of a mouse 2 hours after the intraperitoneal injection of 0.01 c.c. of virulent culture of Type III pneumococcus. The bacteria show well-defined capsules and no evidence of phagocytosis is seen. Many polymorphonuclear and a moderate number of mononuclear leukocytes are present. Gram stain.  $\times 1000$ . Courtesy of the Journal of Experimental Medicine.

FIG. 2. Photomicrograph of a corresponding preparation of the exudate of a mouse 2 hours after receiving the same amount of culture together with 0.5 c.c. of a preparation of the specific enzyme. The bacteria are devoid of capsules. Polymorphonuclear leukocytes predominate and phagocytosis is evident. Gram stain.  $\times 1000$ . Courtesy of the Journal of Experimental Medicine.

FIG. 3. Photomicrograph of a stained film of the peritoneal exudate of a mouse 4 hours after injection with 0.01 c.c. of culture alone. The bacteria are increased in number, encapsulated, and extracellular. The cellular elements are polymorphonuclear and mononuclear leukocytes in about equal numbers. Gram stain.  $\times 1000$ . Courtesy of the Journal of Experimental Medicine.

FIG. 4. Photomicrograph of a corresponding preparation of the exudate of a mouse 4 hours after receiving the same amount of culture together with 0.5 c.c. of a preparation of the specific enzyme. Marked phagocytosis has occurred and only an occasional organism is seen outside the accumulated leukocytes, nearly all of which are of the polymorphonuclear type. Gram stain.  $\times 1000$ . Courtesy of the Journal of Experimental Medicine.

(Differences in the density of the backgrounds of figures 1-4 are due to the use of color screens in the photographic reproductions. This technic, however, alters none of the essential details observed in the original microscopic preparations.)



FIGS. 1-4



ing cells of other, unrelated microbial species. Specifically, it was attempted to discover soil microorganisms that could attack the living cells of Gram positive cocci. To achieve this end, suspensions of living pneumococci, streptococci and staphylococci were added to a soil mixture which was maintained at neutral reactions under aerobic conditions, in the hope that there would develop in the soil sample a microbial flora antagonistic to the Gram positive cocci. In fact, it was possible to isolate from this soil preparation an aerobic sporulating bacillus, belonging to the vast group typified by *Bacillus mesentericus*, which produces a soluble principle extremely toxic for Gram positive bacteria.<sup>6</sup>

This bactericidal principle is abundantly produced when the soil bacillus is grown under strict aerobic conditions in certain peptone media; it can be obtained in solution in an active form free of the bacterial cells which produce it. In fact, several different substances, which all have in common a marked selective bactericidal effect for Gram positive bacteria, have been obtained in solution from peptone cultures of the same bacillus; it is likely that these different active substances are breakdown products of a common mother substance, and result from the manipulations inherent to the technics of extraction and purification. In any case, these different substances exhibit different physiological activities, and their nature and properties will be considered separately.

The bactericidal agent is very soluble in alcohol, acetone, and dioxane. It can be obtained in solution by extraction of an acid precipitate (pH 4.7) of the culture of the soil bacillus with any one of these organic solvents. The bactericidal material is on the contrary very insoluble in ether and in aqueous media; it can be precipitated from the alcoholic solution by diluting the latter with large volumes of aqueous saline. The precipitate can be desiccated and carries the bactericidal activity of the original culture.<sup>13</sup>

The material thus obtained is free of protein. It can be further purified by differential fractionation in alcohol-ether mixtures. The bactericidal material can thus be collected in two fractions: (1) material insoluble in a mixture of one volume of alcohol and fifteen volumes of ether, and (2) material soluble in the same mixture but insoluble in pure ether.<sup>22, 23</sup>

From fraction (1) there were isolated by crystallization from alcohol two crystalline acidic substances which have been designated graminic acid and gramidinic acid. Acetone solutions of fraction (2) have yielded a crystalline neutral substance which has been named gramicidin. The complete chemical structure of these substances is as yet unknown. It can be stated at this time, however, that all of them consist largely of amino acids, probably combined as polypeptides. Gramicidin, which has been most carefully studied, has a molecular weight of about 1400 and contains 2-3 tryptophane residues per molecule; a large percentage of the other amino acids appear to be present in the *d*-(so-called unnatural) form; gramicidin also contains an aliphatic fatty acid, but neither free acid nor basic group (figures 5, 6).

As stated above, graminic acid, gramidinic acid and gramicidin are endowed with bactericidal activity; 0.005 to 0.01 mg. of these substances is sufficient to kill in vitro  $10^9$  pneumococci, or group A streptococci, in two



FIG. 5. Photomicrograph of crystals of gramicidin.  $\times 225$ .

(Reproduced by courtesy of Dr. R. D. Hotchkiss)

hours at  $37^{\circ}$  C. Still smaller amounts inhibit the growth of Gram positive bacteria in nutrient broth. This is particularly striking in the case of pneumococci which fail to grow in broth containing a dilution of 1:1,000,000,000 of the active substance.<sup>13</sup>

Not only pneumococci and streptococci but also other Gram positive organisms such as staphylococci, diphtheria and diphtheroid bacilli, and sporulating bacilli are rapidly killed by the same bactericidal principle, although the amount of the agent required varies slightly from one bacterial



FIG. 6. Photomicrograph of crystals of graminic acid.  $\times 320$ .

(Reproduced by courtesy of Dr. R. D. Hotchkiss)

species to another. On the contrary, the Gram negative bacilli are resistant to graminic acid, gramidinic acid and gramicidin. Recent experiments have established that gonococci and meningococci are more resistant than the Gram positive organisms but more susceptible than the Gram negative bacilli; it is of interest to point out in this respect that, although meningococci and

gonococci react negatively to the Gram stain, they are very different in other respects from the Gram negative bacilli.

The standard test used for estimating the activity in vivo of the preparations of bactericidal substance has consisted in determining the minimal amount of substance which, when injected intraperitoneally within 30 minutes after infection, will protect mice against 10,000 fatal doses of Type I pneumococci.

In spite of the great bactericidal activity which graminic and gramicidin acid exhibit in vitro, these substances appear to be ineffective in vivo. On the contrary, one single dose of 0.001 to 0.002 mg. of gramicidin, injected into the peritoneal cavity, is capable of protecting mice against 10,000 fatal doses of pneumococci or hemolytic streptococci. The material has been found equally effective against infection with five different types of pneumococcus, 11 types of Group A streptococcus and three strains of Group C streptococcus; other types were not tried (table 2).

TABLE II  
Protective Action of Crystalline Fractions of Bactericidal Agent  
(All mice infected with 10,000 fatal doses of Type I Pneumococcus)

Material	Amount	Number of mice	Result		
	mg.				
Graminic acid	0.016	3	D40	D44	D68
Graminic acid	0.008	3	D40	D40	D48
Graminic acid	0.004	3	D40	D40	D40
Graminic acid	0.002	3	D40	D96	D96
Graminic acid	0	3	D24	D40	D40
Gramicidin	0.010	3	S	S	S
Gramicidin	0.005	3	S	S	S
Gramicidin	0.002	3	D61	D114	S
Gramicidin	0.001	3	D45	D46	S
Gramicidin	0	3	D27	D27	D32

S = Survival.

D = Death; the numeral indicates number of hours after infection.

By using larger doses of the bactericidal agent and repeating the treatment on three consecutive days, it has been possible to protect mice against 1,000,000 fatal doses of pneumococcus and to cure mice of a well established infection, even when treatment was administered 6, 12, and 17 hours after injection of the infective dose.<sup>7, 13</sup>

The results which have just been reported demonstrate that gramicidin, when injected into the peritoneal cavity in mice, is very effective against infection with pneumococci and streptococci. However, the same substance when injected intravenously, subcutaneously, or intramuscularly, fails to protect mice against infection with the same organisms. Gramicidin is very insoluble in aqueous media and it is possible that it fails to diffuse and reach

the different foci of infection. This fact may account in part for its failure to act when injected at a site remote from the infected area.

In any case, it is obvious that the insolubility of the material in aqueous media is a great handicap both for experimental studies and for possible use in therapy. It has been recently found that a number of dispersing agents (such as sulphonated and sulphated oils) permit the substance to remain in solution in water even in the presence of electrolytes; ox bile also acts as a particularly effective dispersing agent, 2 c.c. being sufficient to maintain 10 mg. of gramicidin in solution.

Furthermore, it has been possible to extract from cultures of the soil organism which produces gramicidin a form of this substance which is completely soluble in water, without the help of dispersing agent. This soluble fraction is obtained by clarifying an autolysate of the peptone culture by centrifugation and filtration through a Berkefeld candle; the clear filtrate is then adjusted to pH 4.7 and the precipitate separated by centrifugation. This precipitate is again soluble in saline at neutral reactions; it gives the usual protein tests and exhibits marked bactericidal activity. When injected by the intraperitoneal route, 0.2 mg. is sufficient to protect mice against 10,000 fatal doses of pneumococci. Moreover, in a number of instances, it has been possible to cure mice of pneumococcus peritonitis and septicemia by the subcutaneous injection of 2.0 mg. of the same water soluble fraction. The methods of preparation of this new material and the technic of administration to experimental animals have not yet been perfected, so that the results of subcutaneous treatment are still very irregular; they are, however, unequivocal and show that it is possible to extract from cultures of the soil bacillus a form of the bactericidal substance which is more effective *in vivo* than the crystalline material described under the name gramicidin.

Much remains to be learned about the physiological activity of these substances, both upon the bacterial cells and in the mammalian organism. It has been shown that the bactericidal principle in its different forms (graminic acid, gramidinic acid, gramicidin, and the new water soluble fraction) interferes with some of the essential metabolic functions of the susceptible bacterial species.<sup>8</sup> It is also known that gramicidin exhibits a marked toxicity for mice, rabbits, and dogs when administered by the intravenous route, 3 mg./kg. being sufficient to kill a dog within 48 to 72 hours.<sup>24</sup> Any attempt to express the toxicity of the material in terms of its therapeutic efficacy would be misleading at the present time. It must be remembered in this respect that practically all the successful protection tests to date have involved the intraperitoneal treatment of pneumococcus and streptococcus peritonitis in mice; gramicidin has proved ineffective when administered by the intravenous, intramuscular, or subcutaneous route. The few successful results obtained by the subcutaneous administration of the new water soluble fraction are too preliminary and have been too irregular, to warrant generalization.

## DISCUSSION

It may be worth while to contrast again the mechanisms whereby the two types of microbial reagents which have been considered in the present report, protect experimental animals against bacterial infections.

The first group of reagents was obtained by isolating from soil, microorganisms capable of multiplying in solutions of the capsular polysaccharides of the different types of pneumococci. Cultures of these bacilli have yielded soluble enzymes, each one of which hydrolyzes one of the specific polysaccharides. Not only do the polysaccharidases decompose the soluble, isolated polysaccharides, but they also destroy the capsules which surround the virulent pneumococci, and protect animals against pneumococcus infections; these reactions are highly specific, the specificity being determined by the chemical nature of the polysaccharide which constitutes the capsule of the particular type of pneumococcus under consideration. The enzymes are neither bacteriolytic nor bactericidal; by destroying the protective capsular material of the pneumococci, they merely render them susceptible to the phagocytic action of the cells of the infected host.

In some respects, therefore, the polysaccharidases exert upon the infectious process an influence similar to that exerted by the specific anti-pneumococcus sera. Both types of agents prepare the encapsulated bacteria for phagocytosis, the antibodies by specific sensitization, the enzymes by the progress of decapsulation. In the former instance, the reaction is an immunological one whereby the capsular material is altered by union with the type specific antibody; in the latter case, the reaction is an enzymatic one which results in the actual decomposition of the polysaccharides. Neither the enzymes nor the specific antibodies are by themselves bactericidal or bacteriolytic, yet each, by reacting specifically with the capsular substances, exposes the virulent organisms to the phagocytic action of the body tissues.

Gramicidin, the other protective agent described in the present paper, has also been extracted from a sporulating soil bacillus, but does not appear to belong to the class of enzymes. It should rather be considered as a true antiseptic, minute concentrations of which inhibit the growth of the susceptible species in nutrient media, whereas higher concentrations exert an actual killing effect. It is likely therefore that the protective action induced in vivo by this new agent can be explained, in part at least, in terms of its bacteriostatic and bactericidal effect upon the susceptible bacteria.

Whereas the specific enzymes, like the specific antibodies, act upon a product of the bacterial cell, namely the capsular polysaccharide, the new bactericidal agent probably interferes with some essential metabolic function of the invading microorganisms; in this respect, the mechanism of its protective action presents some analogy with that exerted by the sulfanilamide group of drugs, which do not affect the capsular substances of pneumococci, but only inhibit the growth of the bacterial cells.

Gramicidin protects mice against infection with pneumococci, strepto-

cocci, and staphylococci, all bacterial species which are susceptible to it in vitro, and appears therefore to be entirely unspecific in its action. It must be emphasized again, however, that gramicidin is ineffective against Gram negative bacilli and for example fails to protect mice against infection with *Klebsiella pneumoniae*.

It can be said, therefore, that the new bactericidal agent exhibits a specificity of a peculiar order, one which is correlated with the staining characteristics of the bacterial cells. Since the staining properties are necessarily conditioned by chemical and physical characters of cellular structure, it is perhaps permissible to state that the specificity of the bactericidal agent is related to some unidentified structural difference between the Gram positive and the Gram negative cells. An analysis of the mechanism of the bactericidal action may therefore reveal important facts concerning cellular structure, and this knowledge in turn will suggest new avenues of approach to the problems of antiseptics. It is also of obvious importance to establish what are the chemical differences between gramicin acid and gramicidin which determine that only the latter is active in vivo, whereas both are equally active in vitro; this knowledge may give us a clue as to the mechanism which allows an antiseptic to remain active in the presence of animal tissues, and suggest technics for the synthesis of new chemotherapeutic agents.

It is permissible to hope also that one will eventually discover in nature microorganisms capable of attacking other types of pathogens, or their toxic principles. By extracting from cultures of the soil organisms the active antibacterial or antitoxic principles, then determining their nature and the mechanism of their action, the bacteriologist and the chemist may discover new compounds, and new technics for the development of chemotherapy on a rational basis.

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# THE COMPARATIVE EFFECTIVENESS AND TOXICITY OF SULFATHIAZOLE AND SULFAPYRIDINE IN PNEUMOCOCCIC PNEUMONIA \*

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FOLLOWING the discovery that sulfapyridine was an effective agent in treating experimental and clinical infections due to the pneumococcus, chemotherapy of pneumococcic pneumonia has received widespread attention during the past two years. Within this time numerous<sup>1</sup> clinical reports unquestionably have established the therapeutic effectiveness of sulfapyridine in pneumonia. However, it is generally recognized that sulfapyridine therapy is not ideal because nausea and vomiting often interfere with adequate treatment. Furthermore, serious toxic manifestations, such as blood dyscrasias and renal complications, may occur.

Within recent months there has become available a new sulfanilamide derivative, sulfathiazole,‡ which we have used in the treatment of patients suffering with pneumococcic pneumonia at the Philadelphia General Hospital. Sulfathiazole, 2-(p-aminobenzenesulfonamido) thiazole, synthesized by Fosbinder and Walter<sup>2</sup> and Lott and Bergeim,<sup>3</sup> is the thiazole analogue of sulfapyridine. The therapeutic effectiveness of sulfathiazole against experimental pneumococcic infections has been investigated by McKee, Rake, Greep, and Van Dyke<sup>4</sup> and found to be equal to that of sulfapyridine. Van Dyke, Greep, Rake and McKee<sup>5</sup> showed that sulfathiazole administered to mice with their food was no more toxic than sulfapyridine when the dose was kept at therapeutic levels.

In a recent report<sup>6</sup> observations on the pharmacology and toxicology of sulfathiazole in man were discussed. It was found that sulfathiazole was absorbed more rapidly than sulfapyridine from the gastrointestinal tract and was excreted more rapidly in the urine. Following the intravenous administration of sodium sulfathiazole recovery of the drug in urine was practically quantitative. Absorption of sodium sulfathiazole by rectum was slow and only 10 per cent was found in the urine within 24 hours.

The purpose of the present report is to compare the therapeutic effectiveness and toxicity of sulfathiazole and sulfapyridine in the treatment of pneumococcic pneumonia.

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† With the collaboration of Jefferson H. Clark, M. D., and John G. Reinhold, Ph.D. From the Committee for the Study of Pneumonia, Philadelphia General Hospital.

‡ We are indebted to Dr. George A. Harrop, Squibb Institute for Medical Research, New Brunswick, New Jersey, for the sulfathiazole used in this study.

## SELECTION OF CASES

From the beginning of this study (November, 1939) the medical services \* in the hospital were divided into two therapeutic groups, so that approximately an equal number of pneumonia patients received sulfathiazole or sulfapyridine. During this period of five months 152 patients were treated with sulfathiazole and 162 patients with sulfapyridine. In this report, our observations on the first hundred patients from each therapeutic group are presented. Of the 200 patients, 19 (10 sulfathiazole, 9 sulfapyridine) received specific antipneumococcus serum † in addition to chemotherapy.

## DIAGNOSIS

The diagnosis of pneumonia was established by the clinical history and the findings on physical examination. When indicated, the diagnosis was confirmed by roentgen studies. A specific pneumococcus type was recovered from the sputum or blood stream in all patients. Blood cultures were taken in 95 per cent of the cases, but some of these were not obtained until a few hours after treatment had been started. Repeated blood counts and urinalyses were made in all patients. Determinations of free and total drug in the blood were made in all patients receiving sulfathiazole and in most of those treated with sulfapyridine. Other laboratory studies were made as indicated.

## SULFATHIAZOLE DOSAGE

Except in a few patients treated at the beginning of this study we employed the following dose schedule: An initial 3 gm. dose by mouth was repeated in four hours, then followed by 1 gm. every four hours. Several extremely ill patients were given three initial doses of 3 gm. each at four hour intervals. Dosage on this scale maintained an average concentration of free sulfathiazole of about 5 mg. per cent.<sup>6</sup> Treatment was continued until the temperature remained normal for 48 hours along with evidence of clinical improvement. In general, the total dosage was 25 to 40 gm., depending on the physical and laboratory findings in each case. Sodium citrate (or potassium citrate) in an amount equal to that of sulfathiazole was given with each dose of the drug. In certain instances, when a rapid elevation of the blood level of the drug was desired a 5 per cent solution of sulfathiazole sodium (0.06 gm. per kilogram of body weight), was administered, as a supplement to oral therapy. One intravenous dose was usually sufficient to raise the blood level of free sulfathiazole to 8 to 10 mg. per 100 c.c.

\* We wish to express our thanks to the following Chiefs of Service for the clinical facilities they have given us for this study: Dr. R. S. Boles, Dr. H. D. Jump, Dr. T. Klein, Dr. D. W. Kramer, Dr. S. A. Loewenberg, Dr. D. Riesman, Dr. W. E. Robertson, Dr. H. W. Schaffer, Dr. T. G. Schnabel, and Dr. R. G. Torrey.

† The sulfapyridine and serum used in this study were supplied by the Pennsylvania State Department of Health, Pneumonia Control.

## SULFAPYRIDINE DOSAGE

The initial dose was 3 gm. by mouth, followed by 1 gm. every four hours until the required total dosage had been given. A total of 25 to 35 gm. was usually sufficient. As with sulfathiazole therapy the drug was given until the temperature had remained normal for 48 hours and satisfactory clinical improvement was noted. Sodium bicarbonate was given, in an amount equal to that of the drug, to most patients with each dose of sulfapyridine. Sulfapyridine sodium, 5 per cent solution (0.06 gm. per kilogram of body weight) was administered in conjunction with oral therapy when indicated. With sulfathiazole or sulfapyridine therapy at least 2500 c.c. of fluid were given during each 24 hour period.

TABLE I  
Distribution of Types, Bacteriemia, and Mortality Rates

Type	Sulfathiazole Treated				Sulfapyridine Treated			
	All Cases		Bacteriemic Cases		All Cases		Bacteriemic Cases	
	Number	Died	Number	Died	Number	Died	Number	Died
I	17	2	1	1	23	3	3	—
II	6	1	1	1	2	—	—	—
III	25	4	3	1	22	6	3	3
IV	8	1	2	1	4	—	—	—
V	5	—	2	—	8	1	1	1
VI	4	1	1	—	3	—	—	—
VII	9	—	—	—	6	1	2	1
VIII	3	1	—	—	7	—	—	—
IX	—	—	—	—	1	1	—	—
X	1	—	—	—	3	—	—	—
XI	1	1	—	—	—	—	—	—
XII	1	—	1	—	2	—	—	—
XIII	1	—	—	—	1	—	—	—
XIV	9	1	2	—	4	1	1	1
XV	—	—	—	—	2	1	—	—
XVI	2	—	—	—	1	—	—	—
XVII	—	—	—	—	2	1	—	—
XVIII	2	—	—	—	3	—	—	—
XIX	3	—	—	—	1	—	—	—
XX	—	—	—	—	2	—	—	—
XXII	—	—	—	—	2	—	1	—
XXV	1	—	—	—	—	—	—	—
XXVIII	1	—	—	—	1	—	—	—
XXXI	1	—	—	—	—	—	—	—
TOTAL	100	12	13	4	100	15	11	6
MORTALITY PER CENT	12.0		30.8		15.0		54.5	
CORRECTED MORTALITY PER CENT *	7.4		10.0		11.4		37.5	

\* Does not include 9 patients (5 sulfathiazole and 4 sulfapyridine) who died in less than 24 hours after admission; 6 of these cases had bacteriemia (3 sulfathiazole and 3 sulfapyridine).

## SERUM DOSAGE

When sulfathiazole or sulfapyridine had apparently failed to bring about the expected clinical response within 36 to 48 hours the patient was usually given specific serum in addition. The usual preliminary sensitivity tests, conjunctival and intradermal, were always performed. If these were negative after 20 minutes, further intravenous testing with undiluted serum (1 c.c.) was carried out. After waiting 70 minutes for possible untoward

TABLE II  
Analysis of Fatal Cases †  
*Sulfathiazole*

No.	Age	Day of Disease Treatment Begun	Type	Blood Culture	No. of Lobes Involved	Total Drug	Total Serum	Remarks
yrs.	yrs.					gm.	units	
1	37	2	I	Neg.	2	18	100,000	Jaundice (ict. index 250 u.), anuria (B.U.N. 130 mg. %) and delirium tremens on adm. Autopsy: Acute toxic necrosis of liver, cholemic nephrosis, lobar pneumonia.
2*	42	7	I	Pos.	2	3	—	Moribund on adm., died in 8 hrs. Autopsy: Lobar pneumonia.
3	29	5	II	Pos.	3	30	320,000	No response to R. Autopsy: Empyema.
4	77	4	III	Neg.	1	12	—	Diabetes mellitus, cardiac decompensation. No autopsy.
5*	30	6	III	Neg.	2	3	—	Moribund on adm., died in 6 hrs. Autopsy: Lobar pneumonia, toxic deg. of adrenals.
6	77	3	III	Neg.	3	13	100,000	Cardiac decompensation. Autopsy: Broncho-pneumonia, cardiac hypertrophy, portal cirrhosis.
7*	47	10	III	Pos.	2	9	—	Moribund on adm., died in 10 hrs. Autopsy: Lobar pneumonia, luetic aortitis.
8*	42	5	IV	Pos.	2	9	—	Moribund on adm., died in 18 hrs. Autopsy: Lobar pneumonia.
9*	62	3	VI	Neg.	2	6	—	Moribund on adm., died in 15 hrs. Autopsy: Bronchopneumonia, acute coronary occlusion with myocardial infarction.
10	76	4	VIII	Neg.	2	50	100,000	Responded to combined therapy. T. normal for 72 hrs. before death. Cardiac decompensation. No autopsy.
11	52	3	XI	Neg.	1	15	—	Transferred from surgery. Projective vomiting. Intestinal obstruc.? X-ray: Lobar consolidation. No autopsy.
12	40	3	XIV	Neg.	1	22	—	Sputum typing delayed. No response to drug. Autopsy: Lobar pneumonia, nephrosclerosis, cardiac hypertrophy.

\* Patient died within 24 hours after admission.

† Autopsy performed by members of the staff of Pathology of the Laboratories; chief Dr. H. M. Dixon.

TABLE II—*Continued*  
*Sulfapyridine*

No.	Age	Day of Disease Treatment Begun	Type	Blood Culture	No. of Lobes Involved	Total Drug	Total Serum	Remarks
1	78	6	I	Neg.	1	gm. 7	units —	Moribund on adm., died in 28 hrs. No autopsy.
2	49	3	I	Neg.	2	16	—	Responded to R. Sudden death. No autopsy.
3*	55	9	I	Neg.	1	4	—	Moribund on adm., died in 14 hrs. Autopsy: Lobar pneumonia, cardiac hypertrophy.
4	67	2	III	Neg.	1	50	—	Normal T. for 5 days before death. Cardiac decompensation. Autopsy: Broncho-pneumonia, cardiac hypertrophy.
5*	50	8	III	Pos.	1	3	—	Moribund on adm., died in 6 hrs. Autopsy: Lobar pneumonia with abscess, toxic nephrosis.
6*	42	14†	III	Pos.	3	4	—	Moribund on adm., died in 21 hrs. Autopsy: Lobar pneumonia, portal cirrhosis.
7	50	3	III	Neg.	1	15	100,000	No response to R. Autopsy: Lobar pneumonia, marked coronary sclerosis, cardiac fibrosis and nephrosclerosis.
8	64	2	III	Neg.	2	13	—	Responded to R. Sudden death in 38 hours. No autopsy.
9*	49	5	III	Pos.	1	6	—	Moribund on adm., died in 18 hrs. Autopsy: Lobar pneumonia, cardiac hypertrophy and toxic degeneration of adrenals.
10	66	3	V	Pos.	1	26	600,000	No response to R. Alcoholism. Autopsy: Lobar pneumonia and nephrosclerosis.
11	42	8†	VII	Pos.	1	15	100,000	No response to R. Alcoholism, cardiac decompensation. No autopsy.
12	42	6	IX	Neg.	3	26	—	Responded to R. Normal T. for 36 hrs. before death. Autopsy: Lobar pneumonia, cardiac hypertrophy, nephrosclerosis.
13	32	1	XIV	Pos.	1	15	—	Before adm. jumped from third story window. Broken arm, fractured skull? Alcoholism. Moribund throughout hospitalization. No autopsy.
14	40	2	XV	0	2	24	—	Responded to R. Normal T. for 6 days before death. Cardiac decompensation. Autopsy: Lobar pneumonia, cardiac hypertrophy, mitral stenosis.
15	69	8†	XVII	Neg.	2	25	—	Cardiac decompensation. Autopsy: Broncho-pneumonia, bronchogenic ca. rectal carcinoma, cardiac hypertrophy.

reactions, and if none were detected, the patient was given an initial dose of 100,000 units of undiluted serum intravenously followed by further serotherapy when necessary.

## THERAPEUTIC RESULTS

The results of treatment in the two therapeutic groups are shown in table 1. Of the patients treated with sulfathiazole, 12 died. In the sulfapyridine treated group there were 15 deaths. Patients who were moribund on admission and died within 24 hours were included in both therapeutic groups, although they did not provide a fair trial for either drug. Five such patients were treated with sulfathiazole and four with sulfapyridine. If these cases are excluded the corrected mortality becomes 7.4 per cent and 11.4 per cent for the sulfathiazole and sulfapyridine treated groups respectively.

TABLE III  
Mortality According to Race and Sex

Race	Sex	Sulfathiazole Treated			Sulfapyridine Treated		
		Number	Died	Mortality %	Number	Died	Mortality %
White	Male	37	6	16.2	45	8	17.8
	Female	23	2	8.7	27	4	14.8
Negro	Male	29	3	10.3	23	3	13.0
	Female	11	1	9.1	5	—	—

TABLE IV  
Mortality According to Age Groups

Age Group Years	Sulfathiazole Treated			Sulfapyridine Treated		
	Number	Died	Mortality %	Number	Died	Mortality %
12-19	11	—	—	7	—	—
20-29	20	1	5.0	10	—	—
30-39	17	2	11.8	19	1	5.3
40-49	23	4	17.4	25	6	23.0
50-59	13	1	7.7	20	3	15.0
60-69	9	1	11.1	14	4	28.6
70 and over	7	3	42.9	5	1	20.0

Thirteen patients with bacteriemia were treated with sulfathiazole and four of these died. If the three bacteriemic patients dying within 24 hours are excluded the corrected mortality in this subgroup is 10.0 per cent. In the sulfapyridine treated group, 6 of the 11 bacteriemic patients died, and if the three 24 hour cases are excluded the corrected mortality becomes 37.5 per cent. In both therapeutic groups the unusually high incidence of Type III infection has probably raised the mortality (tables 1 and 2). However, of the 10 fatal Type III patients 4 were 24 hour deaths (2 sulfathiazole, 2 sulfapyridine). Therefore, the corrected mortality values are less affected by the high incidence of this type of infection.

In tables 3 and 4 the distribution of cases according to sex, race, and age groups is given with the mortality per cent. In general, these factors are comparable in the two therapeutic groups. Table 5 shows the incidence of mortality in relation to the day of disease when treatment was begun. Although a greater number of sulfathiazole patients were treated during the first three days of the disease, this does not appear to have had a decided influence on the comparative mortality rates of the two therapeutic groups. Of the 12 fatal cases treated with sulfathiazole, seven patients were treated after the third day of the disease and four of the deaths occurred within 24 hours after admission. In the sulfapyridine treated group eight of the 15 deaths occurred in patients treated after the third day of the disease and five of this number died in less than 24 hours after admission.

TABLE V  
Mortality in Relation to Day of Disease on Which Treatment Was Begun

Day of Disease When Treatment Begun	Sulfathiazole Treated		Sulfapyridine Treated	
	Number	Deaths	Number	Deaths
1	13	—	3	1
2	24	1	21	3
3	21	3	19	3
4	14	3	19	0
5	12	2	14	1
6	4	1	9	2
7	6	1	5	—
7+	6	1	10	5

#### INFLUENCE OF TREATMENT ON THE COURSE OF THE DISEASE

Table 6 shows the effect of treatment on the temperature in the two therapeutic groups (all deaths excluded). A critical drop in temperature occurred within 24 hours in 50 per cent of the patients treated with sulfathiazole, as compared to 65.8 per cent of the patients in the sulfapyridine treated group. At the end of 48 hours 88.6 per cent of the patients receiving sulfathiazole showed a critical drop in temperature compared with 95 per cent of the patients treated with sulfapyridine. The temperature fell to normal, within 24 hours, in only 6.8 per cent of the patients in the sulfathiazole treated group and in 21.2 per cent of the patients receiving sulfapyridine. Within 48 hours normal temperatures occurred in 45.4 per cent and 70.6 per cent of patients in the sulfathiazole and sulfapyridine groups respectively. A secondary rise in temperature occurred in 18 patients (6 sulfathiazole, 6.8 per cent; 12 sulfapyridine, 14.1 per cent) and these usually required further drug therapy. Cases in which a diagnosis of drug fever was made are not included in this group. The average number of hospital days for patients in each therapeutic group is practically the same, 13.2 days. Not included in the latter group are all deaths and 27

TABLE VI  
Effect of Treatment on Temperature and Hospital Stay

Critical Fall in Temperature *	Sulfathiazole Treated		Sulfapyridine Treated	
	Number	per cent	Number	per cent
Within 24 hours.....	44	50.0	56	65.8
Within 48 hours.....	34	38.6	25	29.4
Within 72 hours.....	7	8.0	2	2.4
Over 72 hours.....	3	3.4	2	2.4
Temperature at normal level *				
Within 24 hours.....	6	6.8	18	21.2
Within 48 hours.....	34	38.6	42	49.4
Within 72 hours.....	20	22.8	14	16.5
Over 72 hours.....	28	31.8	11	12.9
Secondary Rise in Temperature (above 99° F.) *	6	6.8	12	14.1
Average Stay in Hospital †.....	13.22 days		13.21 days	

\* All deaths excluded.

† Not included in this group are all deaths and patients kept in hospital for further study and treatment of accompanying conditions.

patients (12 sulfathiazole, 15 sulfapyridine) who remained in the hospital for various conditions (empyema, paresis, diabetes mellitus, heart disease, etc.).

As mentioned above, type specific serum was used in addition to chemotherapy in the treatment of 19 patients. The results are shown in table 7.

TABLE VII  
Chemotherapy Plus Serotherapy in 19 Cases  
*Distribution of Types, Bacteriemia, and Mortality*

Type	Sulfathiazole Treated				Sulfapyridine Treated			
	All Cases		Bacteriemia Cases		All Cases		Bacteriemia Cases	
	Number	Died	Number	Died	Number	Died	Number	Died
I	1	1			3		2	
II	2	1	1	1				
III	3	1	1		2	1		
IV	1							
V					1	1	1	1
VII	1				2	1	2	1
VIII	1	1						
XIV	1		1					
XVIII					1			
TOTAL	10	4	3	1	9	3	5	2



Of the 10 cases in the sulfathiazole-serum treated group, four died. In the sulfapyridine-serum treated group of nine patients, three died. This group of 19 patients included eight bacteriemias, with three deaths.

In every instance that serum was used we were of the opinion that drug treatment had apparently failed to bring about the expected clinical response within 36 to 48 hours. We realize that the value of combined therapy is questionable at present, but until sufficient data are presented to prove it definitely less effective than chemotherapy alone we feel justified in the combined use of serum and drug in selected cases. It is our impression that the administration of serum was a deciding factor in the recovery of several patients.

### COMPLICATIONS

The incidence of complications (table 8) in both therapeutic groups was small and comparable. Massive pleural effusion occurred in three patients treated with sulfathiazole and in two patients receiving sulfapyridine. Empyema was present in only three patients, once in the sulfathiazole

TABLE VIII  
Incidence of Complications (200 cases)

Complications	Sulfathiazole treated Incidence per cent	Sulfapyridine treated Incidence per cent
Massive effusion.....	3.0	2.0
Empyema.....	1.0	2.0
Phlebitis.....	—	1.0
Metastatic abscess.....	1.0	—

treated group and twice in patients treated with sulfapyridine. One patient in the sulfapyridine group developed phlebitis and one patient in the sulfathiazole group suffered a metastatic abscess of the lower abdominal wall which was successfully drained.

### TOXIC REACTIONS

The most frequent untoward effects of both drugs (table 9) were nausea and vomiting. Both symptoms appeared usually during the first 24 hours of treatment. The vomiting associated with sulfathiazole therapy was unlike the severe and persistent vomiting caused by sulfapyridine; it was mild and infrequent and was marked by absence of severe nausea between attacks. In four patients receiving sulfapyridine it was necessary to discontinue therapy because of severe vomiting. In no case did nausea or vomiting necessitate discontinuance of sulfathiazole therapy. It is noteworthy that of the 20 cases of vomiting in the sulfathiazole series fully 13 of these (mild vomiting) vomited only once or twice during the entire course of therapy.

Microscopic hematuria was detected in six patients receiving sulfathiazole and ten patients treated with sulfapyridine. Gross hematuria was observed

in only one instance, in a sulfapyridine treated case. No cases of anuria or renal pain were noted in either group. After treatment with sulfathiazole or sulfapyridine, crystals, presumably of these drugs, have occasionally been observed in the urine. A study of the comparative effect of sulfathiazole and sulfapyridine on the kidney is in progress and the findings will be reported at a later date. However, our observations at this time suggest that although there is a rather frequent reduction in kidney function during treatment with these chemotherapeutic agents, the effect appears to be transient. A return to normal even before cessation of therapy usually occurs. Nevertheless, the possibility of serious renal damage from sulfapyridine, and probably from sulfathiazole, must be borne in mind in the light of experimental and clinical reports.<sup>7, 8, 9, and others</sup>

TABLE IX  
Incidence of Toxic Reactions (200 cases)

Toxic Reactions		Sulfathiazole Incidence %	Sulfapyridine Incidence %
Nausea . . . . .		25.0	84.0
Vomiting *	Mild . . . . .	13.0	12.0
	Moderate . . . . .	7.0	40.0
	Severe . . . . .	0.0	4.0
	Total . . . . .	20.0	56.0
Hematuria	Microscopic . . . . .	6.0	10.0
	Gross . . . . .	0.0	1.0
	Total . . . . .	6.0	11.0
Dermatitis . . . . .		4.0	2.0
Drug fever? . . . . .		2.0	4.0
Psychosis? . . . . .		4.0	7.0

\* Includes 15 patients (8 sulfathiazole, 7 sulfapyridine) who were vomiting before treatment was started. Mild—less than three times; Moderate—three or more times; Severe—necessitated stopping drug.

Dermatitis, apparently caused by the administration of these drugs, was noted in four patients (two were maculopapular and two were urticarial) receiving sulfathiazole and in two patients (maculopapular) treated with sulfapyridine. One patient, treated with sulfathiazole, not included in this series, showed a mild conjunctivitis associated with a drug rash.

The question of drug fever is difficult to evaluate in pneumonia patients, although six cases (two sulfathiazole, four sulfapyridine) apparently showed this condition. Likewise, psychosis is difficult to attribute to the use of chemical agents in an acutely febrile disease such as pneumonia. However, we have encountered 11 patients (four sulfathiazole, seven sulfapyridine) whose symptoms appeared to be due to the drug.

Repeated blood studies failed to show any evidence of a marked reduction in hemoglobin, red blood cell or white blood cell counts. There were

no cases of hemolytic anemia or agranulocytosis in either therapeutic group. However, in the majority of cases the white blood cell count tended to drop during the first 48 hours coincident with the drop in temperature in both groups. The red cell count and hemoglobin likewise fell in a number of cases, but in view of the marked dehydration of most of our patients on admission it has been difficult to evaluate this apparent secondary anemia.

Because of the nature of the disease process, no attempt was made to evaluate the production of cyanosis in either therapeutic group. This condition was comparatively infrequent.

### COMMENT

In view of our experience thus far, sulfathiazole and sulfapyridine appear to be equally effective in the treatment of pneumococcal pneumonia. The mortality of 12 per cent (corrected to 7.4 per cent) in the group of 100 sulfathiazole patients and of 15 per cent (corrected to 11.4 per cent) in the comparable sulfapyridine series compares favorably with the previous mortality rate of approximately 35 per cent at the Philadelphia General Hospital<sup>10</sup> in the years preceding the use of these chemotherapeutic agents.

As evidenced by the critical fall in temperature within 24 hours sulfapyridine appeared to be the faster acting drug, although at the end of 72 hours the effect of both drugs on the temperature was practically the same. With either drug the drop in temperature was usually accompanied by a corresponding subjective and objective improvement of the patient. Significantly, the average stay in the hospital was the same in both therapeutic groups, 13.2 days.

The incidence of complications was very low in this series of 200 cases and was approximately the same in both the sulfathiazole and sulfapyridine treated patients.

Nausea and vomiting, which are so distressing and often troublesome with the administration of sulfapyridine, were much less marked in frequency and severity in the sulfathiazole group. Also, there was some evidence that other toxic manifestations of sulfathiazole were less severe.

At this time we are of the opinion that serum is indicated in selected patients who fail to respond to chemotherapy within 36 to 48 hours.

### SUMMARY

1. Sulfathiazole was given to 100 patients with typed pneumococcal pneumonia and a comparable series of 100 patients were treated with sulfapyridine.

2. There were 12 deaths in the sulfathiazole series, five of which were hospitalized for less than 24 hours (corrected mortality 7.4 per cent). In the sulfapyridine series there were 15 deaths, four of which were hospitalized for less than 24 hours (corrected mortality 11.4 per cent).

3. Sulfapyridine brings the temperature down somewhat more rapidly than sulfathiazole, although the average number of hospital days for the two therapeutic groups was the same, 13.2 days.

4. The severity and frequency of nausea and vomiting in the sulfathiazole treated patients was much less than in those patients receiving sulfapyridine. Other toxic manifestations were approximately equal in the two groups and were not severe.

We wish to acknowledge the technical assistance of Miss Beatrice Doak who was detailed for this and related studies on pneumonia by the Pennsylvania State Department of Health, Pneumonia Control.

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# STUDIES IN MUCOUS MEMBRANE HYPERSENSITIVENESS. IV. THE ALLERGIC REACTION IN THE PASSIVELY SENSITIZED MUCOUS MEMBRANES OF THE ILEUM AND COLON IN HUMANS \*

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IN a previous communication<sup>1</sup> the allergic reactions, occurring in the passively sensitized mucous membranes of the stomach, ileum and colon of the Rhesus monkey, were described. Edema, hyperemia and increase in the secretion of mucus characterized all of these reactions. In these features, the reactions in the mucous membranes of the monkey were very similar to those which had been observed in the passively sensitized mucous membrane of the rectum in humans.<sup>2</sup>

The present communication deals with allergic reactions occurring in the passively, locally sensitized mucous membranes of the ileum and colon *in humans*. These studies were made on two non-atopic individuals who gave the following histories:

Patient X was a male, aged 52, who had been operated upon in June 1936 for a carcinoma of the rectosigmoid portion of the colon. A preliminary transverse colostomy was followed by a resection of the involved bowel with primary anastomosis. The mucous membrane of the colostomy at the time of the present studies (April 1937) showed a moderate amount of congestion.

Patient Y was a male, aged 22, who had been operated upon in March 1937, for a perforating, non-suppurative terminal ileitis. A two-stage Mikulicz operation had been performed. The patient presented an exteriorized ileo-colostomy. The mucous membranes of the ileum and colon at the time of the present investigations appeared normal except for a slight amount of congestion.

## TECHNIC

For the study of the allergic reactions in the human ileum and colon the authors employed a technic very similar to that which they had previously used in their investigations on the human rectal mucous membrane.<sup>2</sup> The first step of the procedure consisted of the sensitization of the mucous membranes of the exposed colon and ileum to peanut protein by the intramucosal injections of a human serum containing atopic reagin antibodies for peanut. After an interval, varying from 24 to 36 hours, peanut antigen was fed to the patients on a fasting stomach. Within several minutes an inflammatory reaction developed at each of the sensitized mucous membrane sites indicating the entrance of unaltered peanut protein into the circulation. The reactions

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of the mucous membranes at the sites of sensitization were the result of the union of the circulating peanut antigen with the reagin antibodies to peanut, which had been injected into the mucosa and had remained fixed in these areas.

*A. Passive local sensitization of the mucous membrane of the ileum and colon.*

1. *Sensitizing Serum:* The choice of a peanut serum for sensitization purposes was accidental and was determined by the circumstance that a suitable serum of this type happened to be available at the time. It was obtained from an asthmatic patient who manifested an unusually strong cutaneous reaction to a skin test with peanut antigen. This serum showed a very high titer for reagin antibodies to peanut antigen (1 to 1024 by the dilution method of Coca and Grove<sup>3</sup>). It was used in a dilution of 1 to 10 for sensitizing the mucous membranes in order to prevent the development of a too severe allergic reaction in these tissues.

2. *Sites of Sensitization:* The mucous membrane of the colon in patient X was sensitized about two or three inches from the skin edge of the colostomy. In patient Y, the mucous membranes of both the ileum and the colon were sensitized from one and one-half to two inches from the skin edge. In both subjects cutaneous sites on the arm were also sensitized with the peanut serum for purposes of control and comparison. When the same subject was used repeatedly for different experiments, care was exercised to use different areas of mucous membrane for sensitization.

3. *Technic of Sensitization:* All nuts and similar antigens were excluded from the subject's diet for the duration of the experiment, beginning 24 hours previous to the sensitizing injection. About 0.05 c.c. of a 1:10 dilution of the sensitizing serum was injected into each mucous membrane site. A 27 gauge needle was employed for this purpose. The procedure was not accompanied by any subjective symptoms and was not followed by any bleeding.

*B. Administration of the Protein Meal.*

From 24 to 96 hours after sensitization, the allergic reaction in the bowel was induced by one of the following procedures: (1) Oral administration of the antigen. (2) Introduction of the antigen through a catheter into the lumen of the exposed bowel. (3) Direct application of the antigen on a cotton applicator to the sensitized site of the mucous membrane. The antigen was administered in the form of a peanut "milk," made by dissolving 10 grams of raw ground peanuts in 30 c.c. of water, to which was added one gram of sugar and 0.05 c.c. of oil of cloves.

The details of some of the most important experiments are presented herewith in chronological order.

## STUDIES PERFORMED ON PATIENT X WITH COLOSTOMY

The allergic reaction *induced by oral administration of the antigen.*

*Experiment I.* April 1, 1937. 10:00 a.m. A site on the mucous membrane of the colon and a cutaneous site on the arm are sensitized to peanut by injections of 0.05 c.c. of human serum, containing peanut antibodies, according to the technic described above.

April 3, 1937. 9:45 a.m. The peanut meal is administered orally. 9:50 a.m. The sensitized mucous membrane site is becoming pale and there is an increase in the secretion of mucus over this area. 9:53 a.m. The pallor over the sensitized site is pronounced. It is surrounded by a zone of pink erythema. The remainder of the exposed bowel retains its original congested appearance. 9:55 a.m. The affected area of mucous membrane appears pale pink, is edematous, and presents an oozing surface. It has lost its normal granular appearance. It appears tense and there is an absence of the normal mucous membrane folds. The increase in the secretion of mucus is marked. 9:56 a.m. The patient reports the onset of pruritus at the sensitized cutaneous site on the arm at this time. This is followed within the next four minutes by the complete development of a large wheal and a surrounding erythema which completely cover the sensitized area. 10:00 a.m. A prominent, tense, crescent-shaped, pale, edematous area now covers the sensitized site on the mucous membrane of the colon. Marked secretion of mucus continues from this surface. 10:10 a.m. Edema at the sensitized mucous membrane site is still pronounced and the oozing of mucus continues. 10:14 a.m. The reaction at the mucous membrane site shows signs of subsiding. The mucous membrane folds are beginning to reappear. 10:20 a.m. The edema is rapidly diminishing but the outline of the crescent-shaped edematous area is still clearly visible. 10:25 a.m. The pinkish pallor of the affected site is disappearing. This area still appears tense and feels slightly indurated. 10:30 a.m. The edema is gradually subsiding. 10:40 a.m. The mucous membrane at the sensitized area is slowly regaining its normal granular markings. Some edema is still present. 11:00 a.m. A slight amount of edema may still be detected at the mucous membrane site. 11:12 a.m. The patient reports a recurrence of the pruritus at the cutaneous site on the arm and of the skin in the region of the colostomy. This symptom is mild and transient. 11:20 a.m. Except for a slight degree of edema, the mucous membrane at the sensitized site is almost normal in appearance. Folds are now present in the mucous membrane and its color is approaching that of the surrounding bowel. 11:45 a.m. A slight amount of edema is still detectable at the site of the reaction. Otherwise the bowel is practically normal.

*Experiment II.* The allergic reaction induced by the introduction of the antigen into the exposed lumen of the colon.

April 21, 1937. 9:00 a.m. A site on the mucous membrane of the colon and a cutaneous site on the arm are sensitized according to the technic described above.

April 25, 1937. 10:47 a.m. A rubber catheter is inserted through the colostomy opening into the lumen of the gut for a distance of about 5 inches. Five cubic centimeters of peanut "milk" are then introduced, through the catheter, directly into the lumen of the bowel. 10:51 a.m. The subject reports the onset of pruritus at the sensitized cutaneous site on the arm. Within two minutes a large wheal and surrounding erythema develop at this site. 10:52 a.m. Pallor and edema are evident at the sensitized mucous membrane site of the colon. 10:56 a.m. The edema of the colon site is marked. The normal mucous membrane folds are absent. The area appears tense. The increase in the secretion of mucus is pronounced. 10:56 to 11:30 a.m. The reaction develops in a manner similar to that described in Experiment I. 11:30 a.m. The reaction at the mucous membrane site is beginning to subside. 12:05 a.m. A slight amount of edema is still visible.

*Experiment III.* The allergic reaction induced by the direct application of the antigen to the sensitized area of the mucous membrane.

May 3, 1937. 2:00 p.m. A site on the mucous membrane of the colon and a cutaneous site on the arm are sensitized according to the technic previously described.

May 5, 1937. 5:00 p.m. A cotton applicator is dipped into the peanut "milk" and brushed lightly across the sensitized mucous membrane site of the colon. 5:05 p.m. The subject reports the onset of pruritus at the sensitized cutaneous site on the arm. This is followed by the appearance of erythema at this area within the next minute and by the onset of wheal formation a minute later. 5:05 p.m. A small bleb is present on the surface of the sensitized mucous membrane site of the colon. 5:07 p.m. The mucous membrane site is pale and edematous. 5:11 p.m. Edema and hypersecretion of mucus are pronounced in the affected area of mucous membrane. From this point on the reaction continues to develop in a manner similar to that described in the previous experiments.

### STUDIES PERFORMED ON PATIENT Y WITH ILEO-COLOSTOMY

*Experiment IV.* The allergic reaction induced by the oral administration of the antigen.

May 3, 1937. 2:00 p.m. A cutaneous site on the arm and mucous membrane sites on both the ileum and the colon are sensitized according to the technic described above.

May 5, 1937. 4:50 p.m. The peanut meal is taken orally. 4:54 p.m. The subject notes a transitory burning sensation in the region of the ileo-colostomy. This disappears within one minute. 4:55 p.m. An erythema accompanied by pruritus is noted at the sensitized cutaneous site on the arm. Within 4 minutes a large wheal surrounded by erythema develops in this area. 4:56 p.m. A small bleb, surrounded by pale mucous membrane is present at the sensitized mucous membrane site of the ileum. The colon mucous membrane site remains unchanged at this time. 4:58 p.m. The pallor over the ileum site is spreading. Pallor is also beginning to develop at the colon site. Both mucous membrane sites now show definite edema and hypersecretion of mucus. 5:03 p.m. Both the ileum and colon sites are pale, markedly edematous and protrude several millimeters above the level of the contiguous bowel. The normal mucous membrane folds are absent over these areas which are from 1.5 to 2 cm. in diameter (see figures 1 and 2). 5:10 p.m. The edema at both mucous membrane sites continues to increase. Mucous hypersecretion in these regions is still pronounced. 5:14 p.m. The edematous mucous membrane areas are now from 2½ to 3 centimeters in diameter. Hyperemia has replaced the pallor at these sites. Increased mucous secretion still continues. From this point, the progress of the reactions is the same as in previous experiments.

*Experiment V.* The allergic reaction induced by the introduction of the antigen into the joint lumen of the ileo-colostomy.

May 10, 1937. 11:00 a.m. Mucous membrane sites of the ileum and colon and a cutaneous site are sensitized according to the technic previously described.

May 12, 1937. 12:56 p.m. Four and one-half c.c. of peanut "milk" are introduced into the joint lumen of the ileo-colostomy. 1:00 p.m. Erythema appears at the sensitized cutaneous site on the arm. A large wheal and erythema, accompanied by pruritus, develop within the next five minutes. 1:04 p.m. The ileum and colon sites show a slight pallor. A slight tenseness of the mucous membranes in these areas is also present. 1:05 p.m. The sensitized mucous membrane areas of both the ileum and colon are markedly edematous and bulge as if inflated with air. There is a pronounced excess of mucus secretion from these surfaces. The normal mucous membrane folds over the reacting areas are obliterated by the edema. From this point, the reactions develop in a manner similar to those described in the previous experiments.



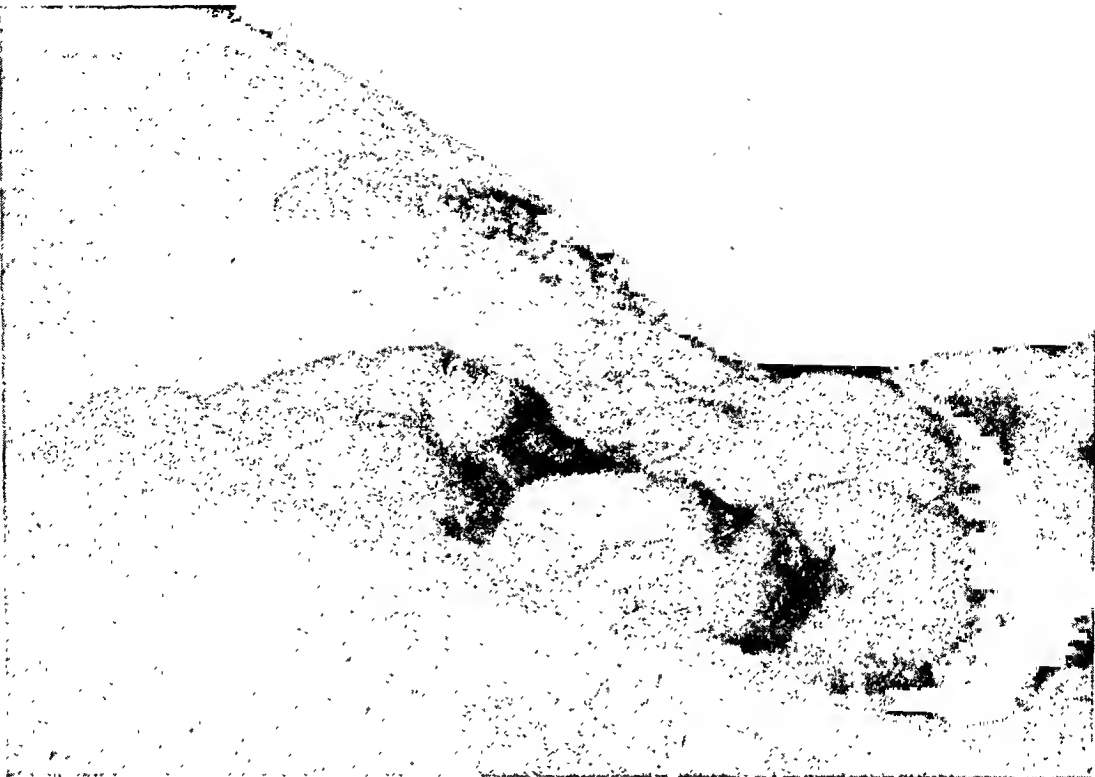


FIG. 1 (Case Y). Normal appearance of mucous membranes of exteriorized ileo-colostomy. Ileostomy on left. Colostomy on right.

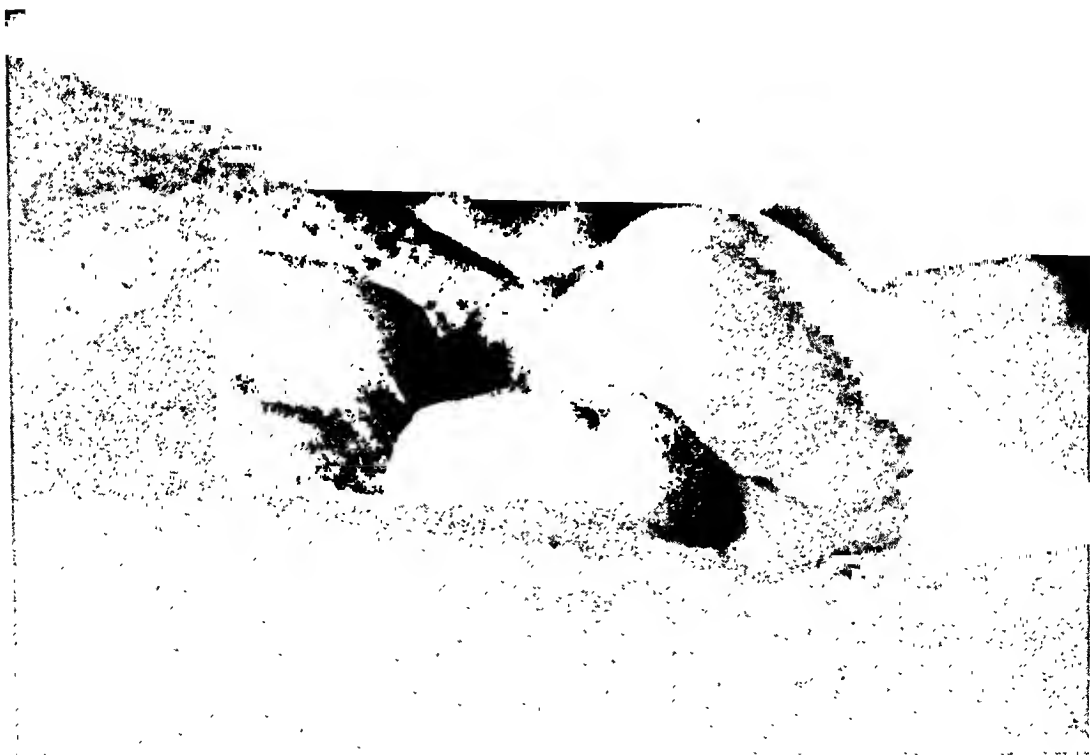


FIG. 2 (Case Y). Ileum and colon sites at height of allergic reactions. Note marked edema of ileum mucous membrane (left) and colon mucous membrane (right) with obliteration of normal mucous membrane folds. Pallor and mucous hypersecretion also observed at this time.

## THE ALLERGIC REACTION AT THE PASSIVELY SENSITIZED MUCOUS MEMBRANE SITES

Pallor of the mucous membrane and an increase in mucous secretion were usually the first objective signs of the allergic reaction as it developed at the sensitized mucous membrane sites. Within one or two minutes the development of edema obliterated the normal mucous membrane folds and markings. The edema usually reached its height within from 15 to 20 minutes and persisted for one or more hours. Although it started at the site of sensitization it diffused to a slight extent into the surrounding area. The pallor which characterized the early part of the reaction was gradually replaced by hyperemia. The reaction was always confined to that region of the mucous membrane which had been sensitized to the specific antigen which was administered.

Examination of the mucus secreted at the site of the reaction failed to reveal an increase in the number of eosinophiles.

Itching and a slight burning sensation of the skin around the colostomy and ileo-colostomy were occasionally reported by the subjects during the course of the reactions.

## DISCUSSION

It has been shown in previous investigations that the mucous membranes of the eye,<sup>4</sup> nose<sup>5</sup> and rectum<sup>2</sup> in humans and the mucous membranes of the stomach, ileum and colon in the Rhesus monkey<sup>1</sup> may be passively and locally sensitized by the injection of human reagin-bearing sera. In the present communication the writers have demonstrated that the mucous membranes of the ileum and colon in humans may be similarly sensitized.

The characteristics of the allergic reaction in the passively sensitized mucous membranes of the ileum and colon are essentially the same as those observed in the sensitized mucous membranes of the stomach, ileum, and colon in the Rhesus monkey and as those noted in the passively sensitized mucous membrane of the rectum in humans. Edema, hyperemia and increased secretion of mucus are the primary features of all of these allergic mucous membrane reactions.

In the present study, the allergic reactions were elicited by the oral or enteral administration of the antigen or by its direct application to the sensitized mucous membrane site.

It is interesting to note that the mere touching of the mucous membrane with a cotton applicator, holding about 0.1 or 0.2 c.c. of peanut "milk," was sufficient to induce a cutaneous reaction in from 4 to 5 minutes. From this incident, one may appreciate what minute amounts of absorbed antigen can produce severe general allergic reactions.

After the administration of the peanut meal the allergic reactions developed at the sensitized cutaneous sites within from 4 to 11 minutes and at the sensitized mucous membrane sites of the ileum and colon within from 5 to 8 minutes. In four of the six experiments, the cutaneous reaction pre-

ceded the mucous membrane reaction in onset by from 1 to 4 minutes. The reactions in both regions, however, seemed to reach their maximum at about the same time. The fact that the mucous membrane, despite its direct contact with the antigen, did not react maximally until the antigen became generally disseminated by way of the circulation had been previously noted by the authors in their rectal mucous membrane studies.<sup>2</sup> It further emphasizes the importance of the general absorption of the antigen in the production of localized allergic reactions of the bowel. It suggests the probability that the most severe crises in gastrointestinal allergy result from excitation of the sensitive shock tissues by the absorbed and circulating offending allergen. The mere application of the antigen to the sensitive wall of the organ does not in itself seem capable of eliciting the maximal allergic reaction of the sensitive mucous membranes.

### CONCLUSIONS

1. The mucous membranes of the ileum and colon in humans can be passively and locally sensitized by the intramucosal injection of human reagin-bearing serum.
2. The allergic reaction can be induced at these sensitized areas by the oral administration of the antigen, by its introduction into any part of the bowel or by its direct application locally to the sensitized mucous membrane sites.
3. The allergic reaction in the passively sensitized mucous membrane of the ileum or colon in humans is characterized by edema, hyperemia and excessive mucus secretion.

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# THE VISCEROSPINAL SYNDROME—A NEW CONCEPT OF VISCEROMOTOR AND SENSORY CHANGES IN RELATION TO DERANGED SPINAL STRUCTURES \*

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NEW concepts in physiology are most often developed in the course of animal and laboratory experimentation. This thesis, however, will trace an apparently new development in physiological thought produced and elaborated through clinical studies since 1925.

The existence of radiation phenomena as the result of radiculitis, "intercostal neuritis," and parietal muscle spasm due to disturbances in the region of the spine, is now generally accepted by clinicians,<sup>1, 2, 3</sup> more particularly by orthopedic surgeons and less universally by the internist. Two chief considerations have been stressed in this "radicular syndrome," viz: (1) cutaneous hyperesthesia and tenderness in the distribution of the spinal segment involved, and (2) muscle spasm or atrophy of muscle groups in the somatic periphery related to this segment. To these concepts may be added a third or *visceral* component.

It is this visceral component and its apparently unrecognized rôle in the body economy that I intend to discuss in this paper. A preliminary consideration of the subject in relation to spinal curvatures was offered in 1933<sup>4</sup> and the term "viscero-spinal syndrome" was used to describe the physiological changes in the viscera produced by essentially the same factors as cause the parietal radiation phenomena. Typical cases were presented in which symptoms of appendicitis, gall-bladder disease, ureteral colic or other manifestations of visceral disease were apparently relieved by correction of a spinal curvature or of the associated myositis. In the main I was convinced that the variations in the visceral symptomatology depended on the various spinal levels involved. Gall-bladder colic and cardiospasm, for example, were shown in some instances to be related to myositis in the middle dorsal area. Symptoms of appendicitis or pelvic inflammation were shown to be definitely associated with irritation of the lower dorsal segments. In these cases physiotherapy and postural correction were sufficient in most instances completely to relieve the patient of the visceral disorder.

This concept was considered somewhat radical in that it pre-supposed certain efferent impulses to the viscera to be initiated by changes in the somatic structures in and about the vertebral column. The actual anatomical pathway for such impulses was denied or at least not sufficiently recognized, except perhaps by a few physiologists.<sup>5, 6</sup> Since then, however, a number of

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investigators have clearly demonstrated the possible anatomical and physiological connections between the autonomic fibers found in the skin, dorsal musculature and vertebral articulations on the one hand and autonomic fibers innervating the viscera on the other.<sup>7</sup> The pathways involved will be described later.

In the preliminary report it was stressed that symptoms produced by visceral changes were not to be confused with hyperesthesia of the skin over the viscus. Intercostal neuralgia produced by osteoarthritis of the spine or by localized myositis near the spine related to the same cord segment was also a factor to be ruled out. Superficial somatic involvement of this type has been described by numerous writers beginning with Dejerine<sup>3</sup> and his "radicular syndrom." Carnett<sup>8</sup> attempted to differentiate "parietal neuralgia from the intra-abdominal lesions which it simulates." Pottenger<sup>9</sup> has repeatedly demonstrated the various skeletal changes brought about by diseases of the lungs and pleura. Furthermore the detailed studies by Gunther and Kerr<sup>10</sup> of the radicular type of pain involving the parietal portions of the body have focused the attention of most clinicians on the *external* manifestation of this radiation phenomenon. Possibly due to the failure of the above writers to visualize an adequate nerve pathway for a visceral involvement no consideration was given to this vital component.

My aim in this presentation is to add to and elaborate upon the observations made in the early studies of this syndrome; to correlate the whole by grouping the different visceral components with the related segmental levels of the nervous system, and to establish the syndrome as important in the differential diagnosis of visceral disease.

More than 400 instances of this syndrome have been encountered. Of these at least 40 per cent have shown multiple manifestations of the syndrome depending on the various segmental levels involved. Most of these patients had been treated without success by one or more physicians who have used the standard medical procedures. To simplify the study an arbitrary grouping of the segmental areas and their related viscera has been made. As far as possible each division is introduced by a description of the particular nervous mechanism involved and completed by a discussion of the physiological changes in the viscus under study.

A brief picture of the fundamental principles of the pertinent neuro-anatomy is offered as a general introduction. This is to do away with repeated descriptions of the subject in each succeeding section.

### NERVOUS MECHANISM

It may clarify the syndrome to describe the probable nerve pathways involved. The apparent simplicity of their arcs makes it difficult to understand the insufficient recognition of their fundamental rôle. In general, afferent impulses from the skin, the dorsal musculature or the articulations of the vertebral column are relayed through the cord and emerge as efferent

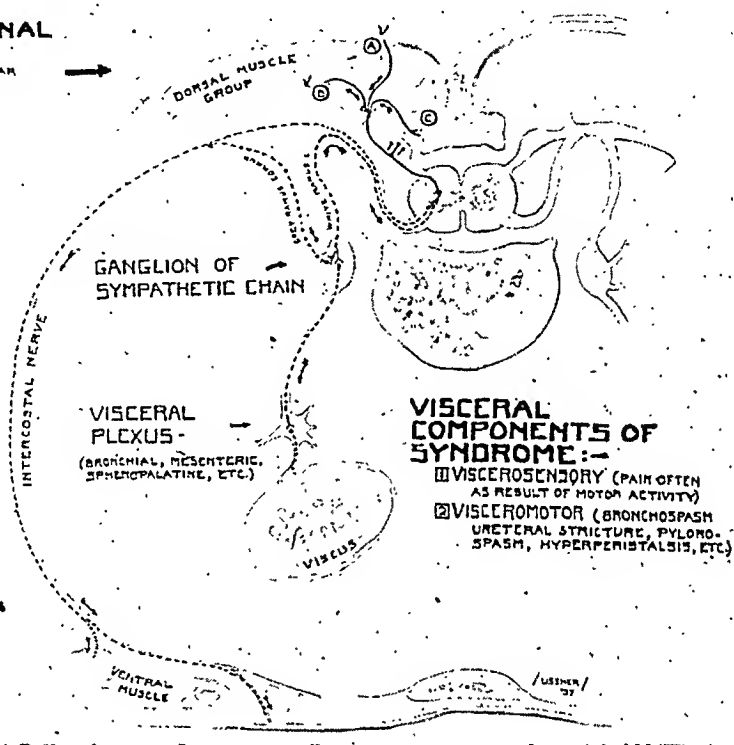
impulses to the viscera. Possibly a more direct route exclusive of the spinal tracts is available but this must be determined by the physiologist. The afferent fibers are mainly of the somatic sensory type and carry impulses from such skin structures as the cutaneous blood vessels (figure 1, A), the secreting glands, and the erector pilae muscles.<sup>9</sup> The afferent impulses (figure 1, B) from the dorsal musculature are also somatic sensory and originate in the muscle spindles.<sup>10</sup> Sympathetic efferent fibers to the muscles are confined in their distribution to the intramuscular blood vessels.<sup>11</sup> It is

### SUGGESTED FOCI OF "SPINAL IRRITABILITY" —

① CUTANEOUS ② MUSCULAR ③ ARTICULAR  
ALSO NERVE TRACTS  
RELAYING IMPULSES  
FROM THESE FOCI  
TO THE RELATED  
VISCUS.

### PERIPHERAL COMPONENTS OF SYNDROME:—

- ① SENSORY (CUTANEOUS HYPER-  
AESTHESIA, INTERCOSTAL  
NEURITIS, ETC.)
- ② MOTOR (MUSCLE SPASM OR ATONY,  
VASOMOTOR CHANGES, ETC.)



### VISCERAL COMPONENTS OF SYNDROME:—

- ① VISCEROSENSORY (PAIN OFTEN  
AS RESULT OF MOTOR ACTIVITY)
- ② VISCEROMOTOR (BRONCHOSPASM,  
URETERAL SPASM, PYLORIC  
SPASM, HYPERPERISTALSIS, ETC.)

FIG. 1. Diagram showing chief components of viscerospinal syndrome. Suggested foci of irritability ("A," "B," "C") are depicted from which afferent impulses are carried to the cord by dorsal nerve roots. Synaptic connections are shown relaying the impulses through the ventral roots to the viscus by way of the visceromotor sympathetic network.

not clear whether afferent impulses originate from these also.<sup>12</sup> The third component of the syndrome (figure 1, C), namely the vertebral articulation, is richly supplied by a sympathetic network containing somatic afferent fibers. Impulses may originate from the peri-articular blood vessels or from the ligamentous attachments. Proprioceptive fibers may be considered an integral part of this group.

These various afferent fibers converge and probably pass into the cord via the dorsal nerve roots and spinal ganglia. Here short synaptic connections allow the afferent impulses to be transmitted to efferent fibers incorporated in the ventral roots of the spinal nerves. Preganglionic fibers now

act as the carriers through the *rami communicantes* to the sympathetic ganglia of the abdominal chain. New synaptic connections in these ganglia allow the transmission of the efferent impulses to the viscera by way of the postganglionic neurons. In some cases the preaortic ganglia, such as the coeliac or mesenteric, act as a final way point for these impulses before the viscus is reached.

It must be remembered that a tremendous literature has grown up concerning the nervous pathways related to the conduction of impulses *from* the viscera. The mechanism of referred pain and changes in the skeletal structures due to visceral disturbances has been widely discussed.<sup>13, 14, 15, 16, 17</sup> It is not within the province of this paper to deal with this phase except to stress the importance of recognizing the viscerospinal syndrome as essentially concerned with a *reversal of the process* that pictures the impulses as originating in a viscus and thence being referred to somatic or skeletal structures.

### HEAD

Orthopedists have repeatedly demonstrated that pain in the occiput and posterior auricular regions may be related to cervical scoliosis and myositis involving the cervical and extreme upper dorsal muscle groups.<sup>18</sup> Their attention, for the most part, has been directed exclusively to the areas innervated by the cervical *somatic* nerve groups, such as the great occipital branches from the second and third cervical nerves. That pain in areas conforming to the distribution of the sphenopalatine and vidian nerves—the orbit, the posterior nasopharynx and the maxillae—may result from the above dorsal and cervical irritations is a point apparently neglected by the orthopedists and the otorhinolaryngologists alike. Sluder and others<sup>19, 20</sup> have minutely described pain caused by direct stimulation of the ciliary, sphenopalatine, and otic ganglia. The clinical causes of such pain, in their viewpoint, were nearby lesions affecting the ganglia; the rôle of distant lesions was not considered. If no cause, such as infection in or about the ganglia, was found, the term “idiopathic neuralgia” was frequently used. Vail<sup>21</sup> has elaborated on Sluder’s studies by describing a neuralgia brought on by sphenoid sinus infection, associated with the vidian nerve and its distribution. This neuralgia is characterized by a “sharp deep pain in the root of the nose radiating in, about, and behind the eye, over the temple to the ear and the mastoid process to the back of the head and neck, and in severe cases passing into the shoulders and arms.” No mention is made of the possibility that a focus of irritability more distant than an adjacent sinus could initiate the train of symptoms. The present study suggests that there are more remote foci which may consist of myositis of the cervical and upper dorsal group of muscles, chilled cutaneous structures in this area, or articular derangements of the cervicodorsal spine. The sympathetic network as well as the somatic nerve groupings act as the probable channels for these rela-

tively distant foci. It has been repeatedly demonstrated in this study that correction of factors causing irritation of these sympathetic fibers results in complete relief of symptoms. Conversely, after such a correction has been made the visceral symptoms may again recur if the myositis, or spinal maladjustment, is allowed to return.

*Case 1.* H. M. C., a moderately obese white married woman of 37.

*Family History:* Irrelevant except for death of father due to Bright's disease.

*Past History:* Usual childhood diseases; pneumonia (type not known) at 6 and 16 years of age. Frequent attacks of tonsillitis followed by a tonsillectomy in 1930. Patient developed rightsided pain shortly after this associated with intrascapular soreness. The pain was thought to be related to her gall-bladder. This was removed along with her appendix. However, both were found to be normal at operation and the patient soon had a moderate recurrence of her symptoms.

*Present Illness:* The patient was referred to the clinic by a dentist in September 1933. Her chief complaint was a dull aching pain in the right upper jaw and temporomandibular joint. The teeth on that side were hypersensitive to dental examination. The pain was fairly constant and had persisted for about a year. At times it became sharp and was noted along the right side of the nose and back of the right eye. She consulted several oculists for her symptoms and also had her right inferior maxillary nerve injected without relief. Two apparently normal teeth were also extracted with similar lack of relief. The patient found aspirin and sedatives of many varieties to be less effective than hot moist towels applied to the back of her neck. On waking in the morning the pain was usually absent. Toward evening the pain was invariably worse than earlier in the day. On questioning, the patient stated that she was worried about her failure to get relief for her condition and that she feared a mental breakdown if the pain continued. Being quite intelligent, she was anxious to convince her husband as well as herself that this condition was not a psychoneurotic manifestation.

*Physical Examination:* The essential findings were as follows: A thick-set, moderately obese woman of 37; dry skin, especially over the extremities; old right rectus scars of abdomen. Examination of the area of complaint (the right face and jaw) showed no definite abnormality either in appearance or in tenderness on pressure. However, a possible hyperesthesia of the skin of the right cheek was noted. (The patient often held, rubbed, or supported her face on that side, and little significance was attached to this finding.)

A sharp cervicodorsal angulation was found and an antero-posterior curve compensating for a lumbar lordosis. A pelvic tilt to the left was also observed. At the seventh cervical spine considerable muscle spasticity of the trapezius was present. Tapping on the cervical prominence with the index finger caused the patient to wince and cry out. She stated that some of her pain in the lower jaw and cheek was reproduced by this procedure. She could not locate the pain definitely but showed evident distress.

*Treatment and Progress:* A quarter-inch total heel lift on the left foot erased most of the lateral scoliosis. Mild postural exercises in the supine position using the infra red ray and massage of the spastic muscles relieved the cervical tenderness within three days. The pain involving the right face and teeth disappeared completely within six days. To facilitate postural correction, weight reduction and thyroid medication were started three months later. There were slight recurrences of pain several times during the next five months when she was particularly fatigued. An additional left heel lift of one quarter inch with continued exercises eradicated the remaining symptoms, and she has remained free of these up to the present writing.



To illustrate the acute involvement of the sphenopalatine network as contrasted with the chronic type a brief summary of one case is herewith presented.

*Case 2.* A. W., a man of 45, was seen at the clinic in December, 1933. He complained of severe pain in the naso-pharynx and was sure that he had an "abscess of the throat." The soft palate and posterior portion of the hard palate were also designated by the patient as areas of soreness. However, no evidence of local hyperemia, abscess or generalized infection was found, although light stroking of the soft palate with a cotton swab was quite painful. A few hours before the onset of symptoms the patient had driven about a hundred miles in a coastal fog with the car window open at his side. He had returned with a stiffness of his neck and a sensation of chilling about the occiput. He paid little attention to these symptoms particularly when the pain in the throat became dominant.

*Treatment and Progress:* As no local evidence of infection was found and appreciable stiffness and tenderness of the neck were present, infra red irradiation and light massage of this area were used. The pain in the palatal areas was markedly intensified by this procedure during the heat treatment. But it diminished and almost completely disappeared in a few minutes after massage of the cervical muscles. The last trace of "sore throat" was gone after a second treatment the following morning.

*Note:* No appreciable scoliosis was found in this patient to account for myositis or articular irritation in the cervical region. Cutaneous chilling in itself may have been of importance as a source of afferent impulses to the sympathetic and sensory network of the palate and naso-pharynx.

#### COMMENT

That a causal relationship exists in the above cases between the deep facial symptomatology and disturbances in and about the cervical region seems reasonable. The exact pathway of these pain impulses is undoubtedly variable and may consist of sensory or sympathetic fibers or both. Once the gap is bridged between external points of sympathetic irritation in the cervico-dorsal region (cutaneous, muscular or articular irritation) and the internal sympathetic network we can easily trace the pathways of the reflex arc. (Figure 1.)

Efferent sympathetic nerve impulses that form this internal network probably pass upward through the middle and superior cervical ganglia, thence along the carotid sheath and are distributed to one or more of the cranial ganglia, i.e., geniculate, otic, sphenopalatine, submaxillary, glossopharyngeal, etc. Synaptic connections within the ganglia thence allow efferent impulses to be distributed to such areas as the orbit, ear or maxillae. The patient experiences pain in these areas through stimulation of the higher centers of the brain by impulses transmitted along the afferent sensory pathways.

In describing vidian neuralgia as due to sphenoid sinus infection irritating sympathetic efferent nerves to the sphenopalatine ganglia, Vail<sup>21</sup> has clearly shown the reflex arcs involved from this point. He traces the impulse as leaving the "sphenopalatine ganglion along the efferent sympathetic nerves, through its orbital branches to the anastomosis which these

have with the terminal branches of the ophthalmic division of the orbit—through the sensory fibers in the great superficial petrosal nerve the stimulus is carried back to the geniculate ganglion. From the ganglion it is carried through the sympathetic efferent nerves of the geniculotympanic branch to the tympanic plexus. There it is taken up by the glossopharyngeal nerve and carried to the higher centers as pain in the ear. A severe stimulus or an overflow passes over the glossopharyngeal and vagus nerves or perhaps through the deep petrosal nerve to the superior cervical sympathetic ganglion and thence to the cervical sensory nerves and is perceived by the higher cortical centers as pain in the neck, shoulder and arm.”

It has been demonstrated in this thesis, however, that the chain of nerve impulses may originate at foci other than the sphenoid sinus, although the end-results may be similar. The pain in the shoulder and neck may in some instances be more closely allied with the cause rather than with the effect of sympathetic nerve irritation. In other words, a cervico-dorsal irritation noticed by the patient as pain at the base of the neck, and observed by the physician as spasm and muscle tenderness of the upper border of the trapezius, may be the initiating factor in the train of symptoms known as vidian or sphenopalatine neuralgia (figure 2). Relief of this irritation by local physiotherapy or postural correction as above has been shown to result in a disappearance of the neuralgia.

That other pathways for this reflex pain must be considered is evident from the complexity of the autonomic and somatic nervous systems of the head and neck. Participation of the glossopharyngeal nerve, the cutaneous sensory branch of the facial nerve and many fibers of the fifth must be considered in reference to varying distributions of pain experienced by the patient.<sup>22</sup>

Interesting conjectures arise when considering the possible rôle of chronic sympathetic nerve irritation in hitherto unexplained trophic disturbances of such structures as the eye, sinuses, ear, etc. It must be admitted, however, that the field is extensive and complicated—that to control the observations adequately many more studies must be completed.

### LUNGS

The chief interest here lies in the possible relationship of the viscerospinal syndrome to bronchoconstriction, or asthma. Emphysema, pleurisy, and lung infections as possibly secondary to derangement of the autonomic nervous system have not been stressed in this particular investigation.

Not infrequently the physician observes a type of patient suffering from bronchial asthma of unexplainable etiology. Extensive protein sensitivity tests may be negative or at least inconclusive. The skin tests may, however, be positive but medical treatment consisting of desensitization to specific proteins and food elimination diets may give no relief. In very rare instances even the drugs used as specific dilators of the bronchial musculature are not sufficient and death may result.

That there is a definite correlation between tonal changes in the sympathetic nervous system and the bronchoconstriction of asthma has been repeatedly demonstrated by many physiologists. It has been shown, for example, that stimulation of the central ends of the thoracic sympathetics or of the communicating rami of the second and third thoracic nerves pro-

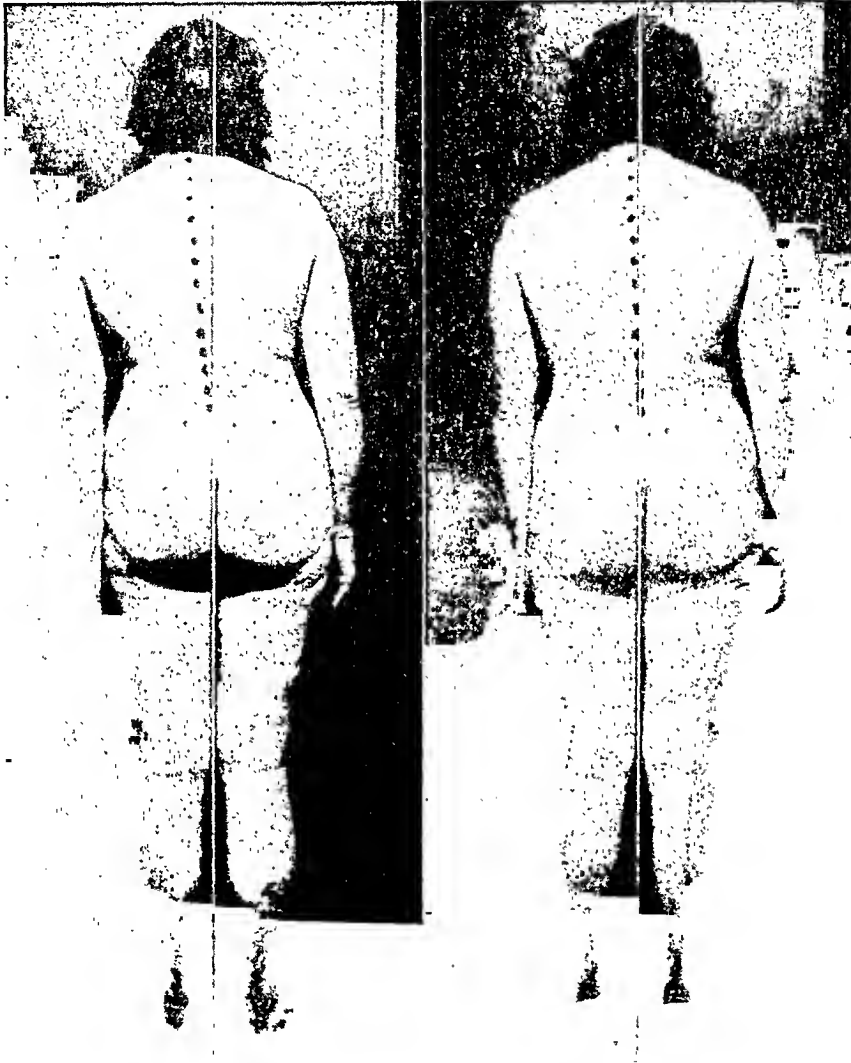


FIG. 2. (Left) Showing uncorrected posture of patient with long standing "sphenopalatine pain" related to cervicodorsal angulation. (Right) Partially corrected position following raise of left heel. Relief of pain noted a few days after correction. Return of symptoms when heel raise was discontinued four months later.

duces bronchoconstriction.<sup>23</sup> Stimulation of the central end of the vagus on the other hand may produce bronchodilatation.<sup>24</sup> It must be remembered that each lung has a bilateral as well as a bisystem supply and that extrinsic as well as intrinsic control is probably exerted by ganglia outside of and also within the bronchial tree.

White<sup>25</sup> attributes the paradoxical results obtained in experimental studies to the "intermingling of parasympathetic and sympathetic neurones in the thoracic vagus and sympathetic ganglia, as well as the relative autonomy of the intrinsic or the extrinsic ganglia of the lungs." He cites his own efforts and those of others to relieve bronchial asthma by interruption of the extrinsic pulmonary nerves. Results have been brilliant in some instances and questionable in others. In any case a consideration of explained and unexplained facts relative to the nervous regulation of bronchial tone leads one to believe that its control is one of the major aims of treatment. It would not therefore be surprising to find that the postulates of the viscerospinal syndrome hold true in certain types of asthma when disturbances of the nervous system in the upper segmental areas of the body occur (figure 1). That certain spinal curvatures, articular derangements and myosites of the dorsal musculature are often associated with the production of asthma has become increasingly evident to me during the past decade.

The possibility of such a relationship was first considered in 1925 when a patient at the New Haven Hospital volunteered the information that while undergoing heat therapy and massage for a muscle strain of his back some months previously he was completely relieved of a distressing asthma from which he had suffered for years. As he stated it, "My lungs were loosened up after a few minutes of the treatment and I was able to breathe freely and without discomfort." The physiotherapy was continued subsequently and the patient apparently had no recurrence of the asthma up to the time of my interview. His story was considered more dramatic than wholly within the facts of the case.

In 1928, however, a ward patient—a marked asthmatic and apparently in extremis—was admitted to my medical service in Providence, R. I. His case history in outline is herewith presented as an introduction to the subsequent studies.

*Case 3.* R. M., a well developed, rather obese Armenian, aged 38, was, when first seen, cold, cyanotic, straining weakly on expiration, and sweating profusely. Two Boston hospitals where he had been a patient several times during the preceding three years reported exhaustive protein sensitivity tests with no positive reactions. His hospitalization periods had ranged from 10 to 22 days, and moderate improvement had resulted from injections of large doses of adrenalin. In the intervals between periods of hospitalization, he had been forced to take 15 to 20 minims of adrenalin a day to obtain partial relief. In the attack, here described, adrenalin, ephedrine, atropine and calcium lactate were administered over a period of 24 hours with little relief, and the patient's heart became irregular in spite of digitalis and general supportive measures. As a last resort, remembering the New Haven incident, the physiotherapy department was requested to attempt a relaxation of the corded muscles of the patient's back. Heat and deep massage were applied to the whole back with especial attention to the region of the third, fourth and fifth dorsal vertebrae. Within eight minutes after this treatment was instituted the patient suddenly coughed up large plugs of mucus and what seemed to be bronchial casts, sank back in bed and began to breathe easily and almost without a wheeze. Six hours later a mild asthmatic attack occurred and was again relieved by a few minutes of massage and heat. Within two days he was dis-

charged in apparently excellent physical condition and advised to return for physiotherapy if attacks recurred.

*Note:* In addition to the above case there were six others ranging from 17 to 45 years of age seen at this hospital clinic who received partial or complete relief through physical therapy. Two patients were not benefited during two weeks of therapy and refused to return. Unfortunately I was unable to follow this first group of patients for more than a few months and do not feel justified in presenting them as typical cases.

*Case 4.* E. S., married, a Spanish woman, aged 33, was seen in the Santa Barbara Cottage Hospital dispensary on July 8, 1932 complaining of severe attacks of asthma during a period of eight years. She appeared acutely ill and unable to walk more than a few steps without resting. Her skin was cyanotic and moist. The lungs showed moderate impairment of resonance at both bases and were filled with large moist and sibilant râles. The heart sounds were distant and of poor quality. Systolic blood pressure 105, diastolic 75. An outstanding feature was a marked kyphosis of her upper spine and an inability to lift her head to the upright position without considerable effort. The muscles in the upper dorsal area were tense and spastic.

The positive findings in her history were as follows: whooping cough, mumps and frequent attacks of conjunctivitis in childhood. In 1925 she was accidentally immersed in cold water during a menstrual period. Following this she developed frequent and severe attacks of asthma. The attacks were brought on or aggravated by chilling drafts, or by dust. The attacks were also worse during the menses. In 1927 she had a tonsillectomy followed by a salpingectomy for "infected tubes." For the ensuing two years the asthma was not very troublesome and the patient believed she was recovering. However, in the fall of 1929 her attacks increased in severity and in frequency (10 to 12 attacks a day and three to five at night). Adrenalin and ephedrine compounds were used in increasing doses with relatively little benefit. Skin tests showed her to be sensitive to a number of foods and fall pollens, but the elimination of the foods did not apparently reduce the number or severity of attacks.

In September 1932 the patient was sent to the hospital physiotherapy department for corrective exercises to modify her kyphosis. Light massage of the upper back and the application of radiant heat were given about three times a week.

*Progress: First month:* The frequency of asthmatic attacks was reduced to two or three per week (previous to treatment they averaged more than 70 a week). The attacks, however, became more acute and developed more suddenly. Large amounts of mucus plugs were expectorated.

*Second month:* The attacks were reduced to one or two per week and seemed to be brought on by chilling in the late afternoon. The time of treatment was changed to the morning hours and improvement was noted.

*Third month:* The attacks continued, about one or two per week, but were milder and were immediately relieved by heat.

*Fourth month:* Patient had but one attack during the whole month. The exercises were stressed and a noticeable postural improvement was observed.

*Fifth month:* Two attacks occurred and in each instance the patient had slept with a window open at her head during cold and foggy weather. A definite swelling of the tissues about her neck and upper edge of the trapezius muscle developed in connection with the attacks. Heat and massage relieved this condition rapidly as well as the bronchoconstriction.

The patient now understands the necessary routine exercises and the general effect of chilling. Her general appearance and health are much improved at the present writing.

*Case 5.* W. C., male, white, aged 7. Seen by Dr. Howard Eder in the summer of 1931. This boy had developed a severe attack of asthma at one year of age—

followed by numerous attacks each year thereafter lasting four to eight hours at a time. The attacks were usually severe enough to keep him in bed for about a week. At three years he had extensive skin tests, all of which were negative except for a mild reaction to acacia. It was noted, however, that the asthma was not particularly aggravated during the flowering of the trees. Food elimination tests were entirely negative. No history of past illnesses except for mumps at three years.

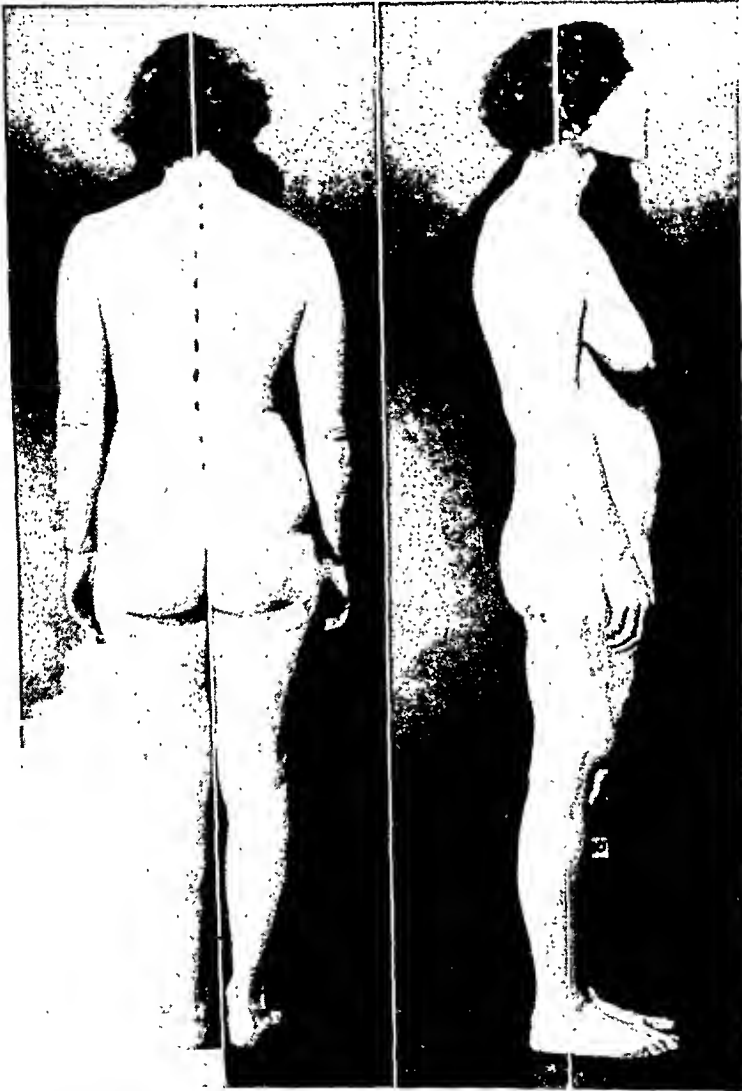


FIG. 3. Antero-posterior and lateral views of severe asthmatic patient before postural correction. Note dorsal scoliosis and kyphosis. Postural exercises were sufficient to maintain adequate relief not previously obtained by medication.

Postural exercises were instituted when it was noted that he had a definite dorsal scoliosis and lumbar lordosis. No heat or massage was used. The asthmatic attacks ceased completely within the first five weeks of exercises and have not recurred for the past 9 years. The boy's posture is markedly improved although a trace of the winged scapulae remains.

It is not clear why a correction of a spinal curvature should produce such a marked change in a boy whose asthma had been present as early as his second year,

for it seems hard to believe that posture is a factor at such an early age of development. However, it is a fact that the usual medical treatment remained almost valueless until postural correction was started.

*Case 6.* E. E., a housewife, white, aged 38 (figure 3), was seen at home in November 1932 during an incapacitating attack of bronchial asthma which was moderately relieved by ephedrine and amytal. Similar attacks had occurred with increasing severity for over a year and the patient dated the onset from a period of overwork at the laundry tubs. Her back had become tired and painful at the time and she had found it difficult to sit or stand "straight." The asthma was worse at the menses or when she was particularly nervous. She was not seen again for six weeks but during this time used prescribed sedatives and ephedrine compounds with very little benefit. The attacks increased in frequency and severity and she was examined at our clinic. The lungs were full of sibilant râles and wheezes. Expirations were markedly prolonged and difficult. Heart sounds of fair quality. Systolic blood pressure 155, diastolic 100. Examination of her back showed a definite dorsal kyphosis and long dorsolumbar scoliosis. The infrascapular musculature was spastic and tender on pressure.

She had suffered most of the childhood diseases and had undergone operations for bilateral inguinal herniae in 1930. Both her father and mother were known to have arteriosclerotic heart disease. In addition her mother and one of two brothers had hay fever and asthma.

Corrective exercises and physical therapy were started immediately after the examination. Within two weeks the patient believed her asthma to be entirely cured and refused to return for the radiant heat and massage. However, she continued faithfully with her exercises and remained free of all asthmatic symptoms for two years. Our physiotherapist made the interesting observation that at the time of her third visit the patient was suffering from a definite attack which was relieved during treatment. Immediately afterward the patient was able to walk home, a distance of more than a mile.

In February 1933, after illness in her family which necessitated considerable nursing attention on her part, she suffered a moderate attack of asthma. This was quickly relieved by the usual physiotherapeutic measures. Since then the patient meets any tendency toward recurrence of attacks by the renewal of her postural exercises.

#### COMMENT

In presenting the above cases of asthma an attempt has been made to keep in mind the numerous etiological possibilities in each individual. It is realized asthma often disappears spontaneously. It is realized that children "outgrow" asthmatic attacks in many instances. Bronchial neuroses do occur, as do reflex asthmatic attacks following disturbances of the sexual apparatus.<sup>7</sup>

However, when a group of persons suffering from long-standing asthma have been given the accepted medical treatment without receiving adequate relief some other procedure must be attempted. If a definite cessation of symptoms follows a new form of therapy this therapy should receive credit for the relief in a certain percentage of the cases. There may be a coincidence in one, in two, or even in three cases but not in a group of 10 or more.

It is evident that in many of the cases studied there was a relationship between asthmatic attacks and chilling. Horton and Brown<sup>26, 27</sup> have re-

ported a number of cases in which there were general as well as local symptoms due to cold allergy. It is their opinion that severe urticaria and asthma may be produced by a histamine-like substance released by the skin when certain individuals are exposed to chilling. Their observations corroborate the findings of Duke,<sup>28</sup> in the study of apparent allergic reactions to cold. Whether or not such a reaction is partially responsible for the asthma in the cases herein reported I am not prepared to say. It is suggested, however, that cold does produce a myositis or spastic contractions of the dorsal muscles. This may cause a change in tonus of the sympathetic nerves to the bronchial tree resulting in a general spasm and closure of the small bronchioles. Mucus and alveolar detritus may fill these stenosed lumina and if the asthmatic condition continues over a long period of time there may occur in certain instances proliferation of fibrous tissue about these inclusions even to the degree of a complete and permanent closure. C. K. Mallory has clearly demonstrated this pathological state in postmortem examinations of patients dying of asthma.

It is my opinion that the majority of bronchoconstrictions in the group presented here are due indirectly to some form of muscle spasm or myositis of the upper dorsal area. This myositis may be produced by direct trauma, by chilling, or as a result of a spinal curvature with irritation of the associated musculature. (Figure 1.) It seems reasonable to suppose that muscle in a state of irritable contractility exerts some effect on the sympathetic network, ganglia or chains in its neighborhood provided there are intercommunicating branches. This intercommunication is well recognized. Therefore I believe in some cases myositis and bronchoconstriction can be definitely correlated through the related nerve pathways.

Another feature is the benefit some patients derive from physical therapy in spite of their sensitivity to specific proteins. This is seen in Case 2, for example, a patient who reacted favorably to treatment though nothing was done to desensitize her or to remove the offending protein by elimination diets. The explanation for this is not clear.

The question arises as to whether the treatment of these cases resembles that offered by the manipulative cults, and the literature has been examined with that point in view. In 1925, Dr. Wm. P. Murphy<sup>29</sup> of Boston collaborated with an osteopath in the study of 20 cases of asthma that had formerly received careful vaccine therapy in the outpatient department of the Peter Bent Brigham Hospital without appreciable benefit. A series of so-called "adjustments" was given by various osteopaths once a week for an average of 70 treatments per patient. It was found in the follow-up study that 10 of the 20 patients had experienced about 50 to 100 per cent relief, either because of fewer attacks or less severe symptoms during attacks. In four of these the attacks were "practically stopped." The remaining patients were not appreciably benefited. It is interesting to note that the osteopaths were not in general accord as to the supposed location or the type of



disturbance involved but the general opinion favored a so-called "lesion" in the region of the fourth and fifth dorsal vertebrae. Treatment consisted of pressure on the transverse processes of these vertebrae and the rib attachments in that area. From our study it seems probable that favorable results were obtained in these cases not through the attack upon a single "lesion" but by obtaining relaxation of the spastic musculature involved. It is quite possible that the osteopath in his relaxation of muscle spasm has obtained results similar to those seen in our patients who showed such definite improvement after physiotherapy. Unless he recognizes the rôle of postural defects in asthma, however, and corrects them along definite orthopedic lines, results will be but temporary.

It would appear then that a suggestive relationship has been established among postural defects, myositis of the upper dorsal areas and bronchospasm. Recurrences of asthma should and do develop in cases where the postural exercises or corrections have been neglected. Conversely the asthma in this type of patient can usually be relieved in a remarkably short time again, and for an indefinite period if physiotherapy, exercises or orthopedic corrections are reinstituted.

### HEART

In any discussion of the neurogenic mechanism of the heart three main nerve groupings should be taken into account:

1. Sensory nerves.
2. Motor nerves related to changes in heart rate.
3. Vasomotor nerves concerned with coronary dilatation or constriction.

The nerves of these three groups are primarily sympathetic and consist of the network connected with the cervical ganglia (superior, middle, and inferior cervical) and with the upper four or five thoracic ganglia. In attempting to interrupt the sensory pathways surgical removal or paravertebral alcohol injections of these ganglia have been carried out with varying results. White<sup>30</sup> in a series of 40 cases of angina pectoris treated by paravertebral injections of alcohol showed that the method was capable of giving excellent results in two-thirds of his patients. In the majority of the remainder the severe forms of angina were converted into milder types which could be easily controlled by medical measures.

When considering the motor pathways, destruction of the accelerator fibers from the stellate and upper thoracic ganglia has also been shown to help in restoring normal rhythm in cases of paroxysmal tachycardia.

In reference to the third components of the extrinsic cardiac nerves, namely the vasomotor nerves involving the coronary circulation and possibly the greater vessels of the heart, numerous experiments would suggest that the caliber of the coronary arteries is directly under their control. There is also probably some indirect effect on the coronary flow through changes in the muscular activity of the heart.<sup>31, 32</sup> Humoral mechanisms must also be considered.

This brief description of the cardiac nerves is given to lay the groundwork for consideration of the viscerospinal syndrome in relation to the heart. The rôle of the sympathetic network in and about the spine and dorsal musculature has apparently not been recognized by investigators in this field. Our clinical observations, however, suggest that in some cases involvement of the parietal structures (skin, intercostal nerves, intercostal muscles) of the upper dorsal segments of the body may be intimately associated with the development of certain cardiac arrhythmias or changes in the coronary circulation. That this assumption seems bold and unorthodox I cannot deny, but it is consistent with observations of the viscerospinal syndrome in other segmental areas of the body.

In this cardiac group have been placed patients showing derangement of vertebral structures (dorsal scoliosis, kyphosis, or myositis) and in addition one or more of the following phenomena: (1) Intercostal neuralgia radiating to the precordial region, and usually designated by the patient as "heart pain." (This parietal manifestation in itself is of little significance but may be mistaken even by the physician for the pain of angina.) (2) Spasticity or atrophy of the pectoral or intercostal muscle groups. (3) Sensory and motor disturbances of the heart itself as indicated by true coronary or anginal pain; by dyspnea (usually transient); by paroxysmal tachycardia or other changes in the heart rate.

Naturally the cardiac symptoms are the most important and yet by their complexity are the most difficult to unravel.

In attempting to carry out an adequate study we are faced with the vagaries of the patient's subjective descriptions of precordial and radiation pain, and of the various neurotic elements in the "heart conscious" patient. In the diagnosis of angina the description of the subjective symptoms is of major importance but the objective findings are often helpful. They consist of the physical signs (changes in pulse, blood pressure, evidence of shock, etc.), cardiographic tracings, and possibly changes in circulation time.

To date the protocols of most of the patients studied in our clinic, as falling into this group are not sufficiently complete for presentation. However, several cases, one of which is offered below, have been under observation for a sufficient length of time to be of some value in this study.

*Case 7.* B. F. N., active, stocky business man of 40.

*Family History:* Father died of "hemorrhage of throat." Mother living but thyrotoxic. One brother has asthma.

*Past History:* Measles, mumps and whooping cough as a child. "Double pneumonia" at 22 years of age. Tonsillectomy at 31 and an appendectomy at 32 years. Bullet wound in right orbit with loss of vision in right eye at 35 years. Periodical vertical headaches every two months for 20 years up to removal of appendix. (He believes, however, that headaches were related to food sensitivity.)

*Present Illness:* The patient was first seen at the clinic in July 1934. At this time he complained of severe pressure in his chest and pain radiating down his left arm. There was also a sensation of fullness and pressure in his occiput and ears. These attacks of distress were fitful, occurring at intervals of two to three weeks and lasting

from one to three days. The attacks were usually accompanied by interscapular back pain. Exercise which produced sweating was found to relieve his symptoms to some extent, but on "cooling off," especially toward evening, they would tend to return. He felt very fatigued during the attacks. He usually smoked 40 cigarettes and drank one to three highballs a day. No particular change in his condition was noted when these were stopped. Often driving a car in cold weather or for long distances brought on the attacks within 24 to 48 hours. This was accompanied at times by severe coughing and vomiting of large amounts of mucus. His appetite was good and his bowels regular. He complained of nocturia two to three times. His sleep was fitful and often required barbiturates.

*Examination:* The essential point in his examination was the kyphosis. He appeared fatigued but outwardly calm. His pharynx was definitely injected from excessive smoking. No evidence of focal infection was evident in his sinuses, teeth or prostate. On examination of the chest wall intercostal tenderness along the fourth rib was noted on the left, also an area of extreme tenderness about the size of a silver dollar near the fourth spinous process. Some rigidity of the long dorsal muscles upward from this point and along the left border of the spine was found. Marked dorsal kyphosis and a lateral cervicodorsal curve apparently contributed to this area of irritation. A pelvic tilt to the left may have been another factor in the production of the lateral curvature. His lungs were clear except for occasional sibilant râles and wheezes. Percussion did not reveal cardiac enlargement although an orthodiagram suggested left ventricular hypertrophy and a Danzer ratio of 0.50. The sounds were of good quality. No murmurs were audible. His apical and radial pulses were 76. The systolic blood pressure was 140, the diastolic 95. His exercise tolerance was good. Electrocardiographic studies showed a moderate left axis deviation. A slight elevation of the S-T<sub>1</sub> and S-T<sub>2</sub> segments was evident. T<sub>3</sub> was inverted. Except for a relaxed abdomen, no gross abnormalities were noted in the remainder of his examination. The reflexes were within normal limits throughout.

*Laboratory:* The blood picture, including the Wassermann test, was negative. The urine showed a faint trace of albumin and occasional hyaline cast on repeated specimens. Roentgenograms of the gastrointestinal tract in August 1934 showed a hypertonic, steer-horn type of stomach, but no other abnormalities were noted. The basal metabolic rate was +10.

*Treatment and Progress:* Nitroglycerin and codeine were given for precordial pain without appreciably influencing the course of the attacks. Saturated solution of potassium iodide produced some possible benefit, but the attacks persisted. Postural exercises were instituted for the dorsal curvature of the spine, but the patient did not adhere to his program. Shortly after this he returned from a week's trip to Seattle with a report of having suffered there a severe anginal type of pain and dyspnea. This persisted until some manipulative procedure by an osteopath gave him relief. The treatment was apparently directed toward the upper dorsal spine. A milder attack the following day was relieved in the same manner.

No evidence of coronary occlusion was found by electrocardiographic studies at our clinic three days after this episode.

#### ALIMENTARY CANAL

One of the most interesting applications of the viscerospinal syndrome is found in disturbances of the gastrointestinal tract. In 1933 I presented a preliminary report<sup>4</sup> in which it was shown that spinal curvatures involving the mid-dorsal spine could be associated in some instances with sensory and motor disturbances of the stomach and intestines. Subjectively these consisted of colicky pain, sense of fullness, bloating, and nausea. The motor

element was found in hyperperistalsis of the intestines, pylorospasm, vomiting (with or without nausea) and spastic constipation. A number of illustrative cases were reported wherein correction of the offending scoliosis had resulted in relief of symptoms.

Following this preliminary report over 200 cases illustrating this segmental response have been observed in the clinics and dispensaries of Santa Barbara. In most instances the syndrome was primarily related to the alimentary tract but involvement of other segmental areas of the body was found. In other words spastic constipation due to a lumbar myositis might be accompanied by a sphenopalatine neuralgia related to a cervical scoliosis, both symptoms in turn due to responses at different segmental levels to double scoliotic curves.

In this presentation it would be of value to elaborate more fully on the individual sections of the alimentary tract, and to add the newer observations related thereto. For convenience of study, I shall divide the tract into four parts, viz., the esophagus, the stomach, the small and large intestines, and the sigmoid and rectum.\*

*The Esophagus.* In this study the esophagus acts as a transitional link between the viscera of the chest and the viscera of the abdomen as indicated by its sympathetic and parasympathetic nerve supply. In tracing the autonomic pathways to the heart and also to the bronchial tree it was noted that most of the sympathetic fibers were derived from the upper thoracic and lower cervical ganglia.<sup>7</sup> The parasympathetic passed through the vagus. Essentially the same neurological pathways are found in the innervation of the esophagus. Branches from the inferior cervical ganglion, from the upper four or five thoracic ganglia and from the greater splanchnic nerve form the sympathetic network. The vagus supplies the parasympathetic fibers.

As we are primarily interested in the clinical application of the viscerospinal syndrome the effect of stimulation of these nerves is of interest. Cardiospasm or achalasia of the cardiac sphincter of the esophagus is produced by such stimulation. Experimental studies, however, are not in full accord as to the exact rôle of either the vagus or the sympathetic elements. The vagus like the sympathetic supply to the cardiac sphincter includes both motor and inhibitory fibers. If the muscle is relaxed or in a state of low tonus, vagus stimulation results in contraction. If the sphincter is closed it results in relaxation thus opening the cardiac orifice.<sup>34</sup>

Four cases of cardiospasm have been classified in our series under the viscerospinal grouping. Three had symptoms of concomitant autonomic nerve disturbances related to the upper dorsal segments or other segmental

\* In considering additional applications of the syndrome, I believe a study of the extrinsic and intrinsic secretions of the pancreas would be of value. The pancreas is richly supplied by autonomic fibers. De Takats and Cuthbert<sup>38</sup> have shown that sugar tolerance has increased 60 per cent in dogs following sympathetic denervation and suggest that a direct inhibitory effect on the secretion of insulin is probable in these instances. Mellanby<sup>39</sup> in very complete studies of pancreatic secretion has demonstrated the effect of vagus stimulation which increases the trypsin and amylase content of the pancreatic juice.

areas affected by the same postural defects. In the remaining patient the cardiospasm was the outstanding complaint.

*Case 8.* White, male, aged 37 (previously reported in 1933 in relation to gastro-intestinal and genito-urinary disturbances of viscerospinal type). The chief complaints during the past two years (1936-1937) were frequent attacks in which solid food seemed to "stick" just before passing into the stomach. At times he was forced to regurgitate food by touching the pharynx before relief was obtained from the accompanying pain. Large amounts of collected mucus along with the food bolus were thus evacuated, but a feeling of discomfort and soreness in the lower sternal area often remained. He noticed that the attacks were most severe shortly after playing golf and taking a shower. They seemed to be related to some chilling and discomfort in the upper back and neck. The patient noticed that by drinking warm liquids quickly and in large amounts he was often able to forestall the painful "sticking" sensations caused by heavier foods. Part way through a meal most of the symptoms tended to disappear. Fatigue and nervousness added to the severity of the attacks.

Fluoroscopic examination with ingestion of a thickened barium meal showed a smooth spastic constriction of the esophagus several centimeters above the cardia which allowed the meal to pass with difficulty. A column of barium remained above this constriction for several minutes and the patient said he experienced the usual "sticking" sensation in his lower sternal region. No evidence of extrinsic or intrinsic tumor masses was visualized.

Examination of the upper dorsal area showed a moderate kyphosis and a high interscapular angulation. Pressure on the second and third dorsal spinous processes elicited considerable tenderness. Spasticity of the interscapular muscle groups was found, particularly on the left. There was also definite tenderness on pressure along the third and fourth intercostal nerves on the right.

Postural exercises aimed to correct a right shoulder drop and resulting dorsal scoliosis were sufficient to relieve most of the interscapular myositis and intercostal pain. Shortly thereafter the attacks of cardiospasm subsided. No medication was used in the form of sedatives or antispasmodics although a more rapid recovery would probably have resulted with such aid.

It is interesting to note that this patient has been under observation for the past eight years by our orthopedic and physiotherapy departments. His dorsal skeletal structures were found to be easily deranged due to a mobile vertebral column. Unless adequate postural exercises were adhered to along with the necessary heel corrections there was a return of scoliotic and antero-posterior curves. This in turn produced local myosites and radiation phenomena as described elsewhere.

#### COMMENT

It must be remembered that the diagnosis of cardiospasm or achalasia of viscerospinal origin is to be made only after other intrinsic or extrinsic etiologic factors have been ruled out. Neoplasms in the esophageal wall or impinging on its nerve supply, ulcers near the sphincter, foreign bodies within the lumen, neuroses and hysterical manifestations are all to be considered in making the diagnosis. However, in a "neurotic" patient with exaggerated nervous manifestations it does not follow that the basic autonomic disturbance in the upper thoracic segments is to be ignored. It should be recognized that anxiety and nerve tension can act as the sparks to initiate other physiological changes in an already irritated segmental level.

*The Stomach and Pylorus.* The second division of the alimentary tract in relation to the syndrome consists of the stomach and pylorus. Here again

the vagus supplies the parasympathetic fibers and the splanchnic nerves ending in the coeliac network supply the sympathetic fibers. The latter are derived chiefly from the fifth to the eleventh pairs of thoracic white rami. Conflicting opinions of investigators have been expressed as to the effect of stimulation of these nerves, but suffice it to say that disturbances in gastric



FIG. 4. Antero-posterior and lateral views of patient with pylorospasm of "viscero-spinal" type. Note pelvic tilt producing lumbar scoliosis and secondary curves in dorsal area. Lumbar lordosis and compensatory kyphosis shown in lateral view. Correction made by right heel raise and postural exercises. Relief of pylorospasm complete and lasting.

motility and in the tone of the pyloric sphincter are produced in all probability by either.<sup>35</sup> Furthermore as clinicians we are particularly concerned with the effects produced by spinal curvatures, myositis, osteoarthritis, etc., in the mid dorsal and lower spine in relation to these viscera and not with the predominance of one or the other of the nerve groups. (Figures 4 and 5.)

Pylorospasm has been the chief objective finding, while nausea, a sense of epigastric fullness, gaseous eructation, colicky pain and vomiting have been most frequently noted by the patient. Usually some points of tenderness along the spinous processes or laterally in the mid-dorsal musculature

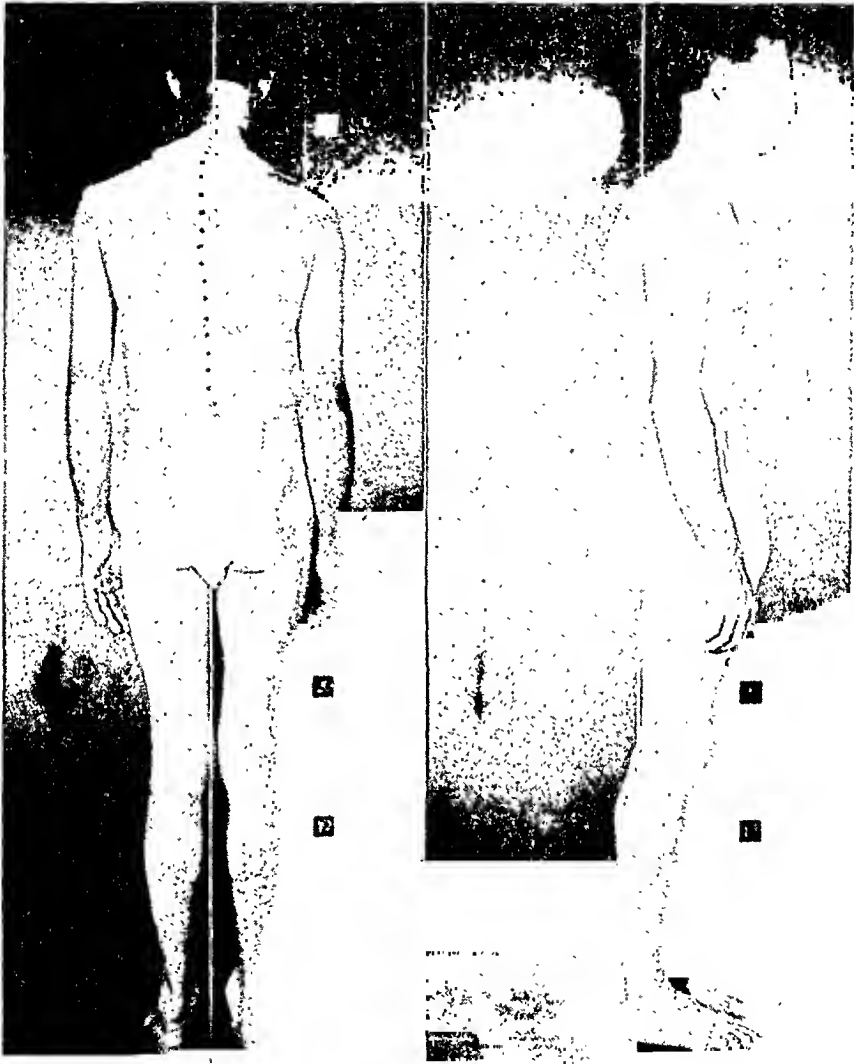


FIG. 5. Postural deformity related to pylorospasm. Corrected by exercises and resulting in relief of long standing symptoms.

have been found. Intercostal tenderness radiating from this point is common. The patient may associate his epigastric symptoms with pain between his scapulae. Hyperesthesia of the skin may be suggested by the complaints of clothing being especially irritating in this area. In many instances the previous treatment has consisted of ulcer management. Antispasmodics and sedatives have also been used particularly where marked pylorospasm was

present (Case 9). In general, results have been disappointing and the patient has made the usual medical rounds for relief.

When all other factors contributory to an ulcer history or pylorospasm were ruled out by roentgenograms or laboratory examinations the patient with the suspected viscerospinal disturbance was put on a therapeutic test. This consisted of a correction of the postural defect, of the articular irritation, or of the myositis related to the mid-dorsal area. Physiotherapy including local infra red irradiation and massage was used in some cases to speed up the mechanism of correction. If without medication the symptoms of pyloric obstruction or gastric irritation disappeared for a sufficient period the patient was considered with reservations a candidate for the viscerospinal classification. Further confirmation was often found in the return of symptoms on reformation of a dorsal scoliotic curve. This occurred in some instances, for example, as a result of not wearing a required heel raise or not maintaining an adequate postural regime. (Figure 4.) Still further proof was gathered in some cases in which local physiotherapy had repeatedly produced immediate yet not lasting relief of gastric symptoms and which subsequently obtained extended relief by orthopedic correction of the spinal irritation.

In some of the following case reports segmental distributions other than that of the stomach and pylorus were involved but the chief complaint was directed to the upper alimentary tract.

*Case 9.* Mrs. K. McC., a moderately obese woman of 38, telephone operator.

*Family History:* Father died of tuberculosis. Husband ill with same infection.

*Past History:* Usual childhood diseases. "Double pneumonia" 1919. Appendectomy and resection of left Fallopian tube 1925. Diagnosis of chronic salpingitis, 1932. Injection of external hemorrhoids, July 1934.

*Present Illness:* Gastrointestinal complaints were a feature during observation in the Santa Barbara Clinic for 14 years up to the time of my first examination in September 1934. (Patient previously was treated by four internists for "colitis," "pain in the right lower quadrant," "constipation," "sour stomach," "pylorospasm" and "peptic ulcer.") At this time her chief complaint was epigastric fullness and distress lasting some three to four hours after eating. She believed it was difficult for the food to pass out of the stomach and was awakened at night by the epigastric distress. Her symptoms were often accompanied by occipital headache. A rather stubborn spastic constipation was also present.

*Laboratory:* Repeated Wassermann and routine blood examinations were found to be negative. The stools were negative for occult or gross blood during observation over a period of 10 years. There were no urinary findings of note. Roentgen studies of the gastrointestinal tract in 1927 suggested a possibility of a prepyloric lesion provided "the clinical history and gastric analysis confirmed." Two additional series were studied in the interval between 1927 and 1934 outside the clinic and no evidence of peptic ulcer was found. In 1934 detailed roentgenological studies were again made by Dr. D. M. Clark at which time a marked pylorospasm was found which persisted for a considerable time after the ingestion of barium. There was no evidence of an ulcer niche or of any characteristic deformity. The gall-bladder was negative. A gastric analysis was refused by the patient at this time (although one analysis, according to the patient, done in Los Angeles in 1925, showed a low acid reading.



*Examination:* A rather well developed woman of 38, who appeared fatigued and in some distress. A refractive error was corrected by glasses. Her teeth showed moderate need for repair. Her lungs were clear. Her heart sounds were lacking in tone. The systolic blood pressure was 130, diastolic 80. On palpation of the abdomen some resistance was noted in the epigastrium and the patient complained of slight nausea. No masses or particular tenderness were noted. On examination of the back an antero-posterior and lateral angulation was noted in the region of the fourth and sixth dorsal spines. A fairly good correction of this lateral curve was obtained by a half inch lift on the left heel. The dorsal kyphosis apparently resulted as a compensation for her lumbar lordosis.

*Treatment and Progress:* Medication directed toward alleviating the gastric distress and pylorospasm was instituted from the beginning. Tincture of belladonna, barbiturate and alkaline powders were used for a period of six months. In addition a modified ulcer program was maintained. No mental or family maladjustment could be found, but several vacations were prescribed away from her local environment. These measures proved to be ineffective—in fact her symptoms were aggravated by walking or riding in a car. Some complaint of pain in the interscapular area prompted a further consideration of her postural defects and a heel lift was prescribed on the left. A definite decrease in the back pain followed and along with it an improvement in the gastrointestinal symptoms. However, she still awakened several times in the early morning with back pain and epigastric fullness. Bed boards and postural exercises by the orthopedic department were then recommended and the symptoms disappeared completely.

All medication was stopped but the exercises were continued. Up to the present writing more than a year has elapsed without a recurrence of gastric distress or pylorospasm. The constipation which was a fairly constant complaint is also gone.

*The Small and Large Intestines.* An arbitrary division of the alimentary canal is made here although an anatomical division of the nerve supply to the pyloric portion of the duodenum and the sigmoidal portion of the colon cannot be entirely divorced from the connecting intestinal tract. This is done for two reasons. In the first place the innervation of the small and large bowel is primarily from a lower segmental plane than is the innervation of the stomach, and from a higher plane than that of the sigmoid. In the second place a clinical division of the tract is necessary on the basis of symptomatology. By far the most frequent complaints noted in this study have been directly related to the intestinal tract. In my preliminary report I suggested that the terms "chronic appendicitis," "intestinal colic," "colitis" were sometimes wrongfully used by internists and surgeons alike when physiological changes in these viscera were due to extrinsic nerve irritation, and not due to pathological changes in the viscera themselves. It was shown that many operations for "chronic appendicitis" had been performed uselessly and without relief of symptoms when this vital point was insufficiently recognized. Carnett<sup>8</sup> had previously determined the results of a series of operations for chronic appendicitis done by a large group of capable surgeons and found that in a fairly high percentage, the patients were not relieved by the operation. He concluded that operative failure in many instances was due to the confusion existing in the mind of the operator between parietal pain (intercostal neuralgia) and pain caused by a pathological viscus

beneath. This was a good point as far as it went but I maintained that in addition to this somatic neuralgia radiating from the spine, actual changes in visceral function were produced by essentially the same mechanism. Colicky pain effected by the contraction of a hypertonic gut on imprisoned gas was shown to be related to spinal curvatures or associated myositis. Surgical confirmation of the syndrome was soon found when Wills and Atsatt<sup>36</sup> presented evidence of localized visceral irritation and spastic bowel paralysis following trauma of the lumbar muscles. They described several cases in which external or parietal neuralgias were accompanied by actual visceral changes.

The majority of patients that I have classified under this particular viscerospinal grouping have suffered no acute trauma to the related spinal structures. Usually they give a history of recurrent back pain in the lower dorsal or upper lumbar region. On examination angulation of the spine with or without demonstrable muscle rigidity is often present. A lumbar lordosis is probably the most frequent spinal curvature observed. Again as I have shown in the segments related to the lungs, heart, esophagus, etc., the correction of the postural defect has resulted in relief of the intestinal disturbances. Postural exercises, heel raises on the short side, supportive physiotherapy have all contributed to the result. At least 40 patients have been spared operations for "chronic appendicitis" in our own series due to the recognition of these radiation phenomena. Full coöperation of the surgical and orthopedic departments has made this possible.

*Case 10.* M. E. S., auto mechanic, aged 27, referred from the endocrine department of the clinic May 31, 1933.

*Past History:* The family and past histories were irrelevant except for attacks of "chronic appendicitis" for two years.

*Present Illness:* The patient complained of general discomfort in the right lower quadrant with slight transient pain when markedly constipated. The constipation was quite persistent and required cathartics once or twice a week in spite of dietary regulations and habit programs for several years. A numb feeling below the right shoulder was a recent complaint.

The patient was of the opinion that an operation for his "chronic appendicitis" would probably help his constipation.

*Examination:* A tall, well developed young man with a moderate exophthalmos and conjunctival redness. There was no evidence of disease of the heart or lungs. There was a slight hyperesthesia of the right lower abdomen as compared with the left. No muscle rigidity was noted. Examination of the back revealed a definite dorso-lumbar curve, antero-posterior as well as lateral. The right leg was one half inch short, producing a pelvic tilt to the right. Correction of this shortening produced a fair realignment of the dorso-lumbar spine and erased the angulation in this area.

*Laboratory:* The blood examination including the Wassermann reaction was negative, as was a single urine specimen. No stool specimen was examined.

*Treatment and Progress:* No medication was given, but a half-inch total right heel lift was prescribed for the dorso-lumbar curve. Within two weeks the subscapular numbness and the discomfort in the right lower abdomen disappeared. There was also a complete relief of his spastic constipation although no mention of such a possibility was made to the patient. During the following year the patient maintained his freedom from symptoms referable to the lower gastrointestinal tract.

## COMMENT

Controlled observation of the complex extrinsic and intrinsic factors governing intestinal activity is difficult. The vagaries of neuroses, nervous tension, allergies, ulcers of the gastrointestinal tract, indigestion, and allied factors must all be considered in relation to the viscerospinal syndrome.<sup>37</sup> Roentgenograms may or may not be of value. Placebos and unrelated therapy must be used to rule out psychic elements. Weiss' technic<sup>33</sup> of injecting the cutaneous area of maximum pain with a local anesthetic has also been used with good effect in making the distinction between actual and imaginary abdominal distress. Subjective complaints of bloating and fairly well localized gaseous distention are quite important provided an adequate control is maintained. Added confirmation of the syndrome is offered when relief is obtained by such a measure as simple postural correction without local physical therapy.

*The Sigmoid and Rectum.* Spasm of the rectal sphincter or inhibition of the musculature of the sigmoid and rectum producing constipation are the chief functional disturbances involved here.

To summarize briefly the nervous pathways it must be remembered that three divisions of the anal canal are to be considered: (1) the lower portion of the sigmoid; (2) the internal sphincter; and (3) the external sphincter and its muscle group. The latter is primarily under voluntary control. The internal sphincter is supplied by the sympathetic and parasympathetic nerves as is the sigmoid and descending portion of the colon. Without going into the neuro-anatomy in detail it may be stated that the hypogastric and pelvic plexuses which supply the sigmoid and anal canal receive autonomic fibers from rami related to the lower lumbar and sacral segments.

Theoretically, in common with the upper segmental areas, irritation of the peripheral afferent sympathetic fibers due to lower lumbar myositis, articular dysfunction, or tortipelvis produces definite disturbances in rectal elimination. Constipation should be the most common finding, as expulsive power cannot be voluntarily controlled by the inner sphincter even though the external sphincter can adequately relax. Conversely excessive peristalsis with its expulsive action in the sigmoid region due to extrinsic nerve irritation is automatically controlled by the voluntary tonus of the external sphincter even though the inner sphincter be completely relaxed.

These theoretical considerations have been borne out repeatedly by clinical observations. Spastic constipation associated with low lumbar irritability has been shown to disappear after correction of one or more derangements of the lower lumbar or sacral areas (figure 6). Very often a pelvic tilt due to a short leg or actual asymmetry of the pelvic girdle can be remedied by a heel lift on the short side. This simple procedure without application of other therapy has produced lasting relief of intractable constipation in a considerable number of cases. (The word 'intractable' is used to denote those cases where roughage, fruit juices, mineral oils, habit training, seda-

tives, etc., have been used with little or no benefit.) The lumbar region is the site of most primary curves<sup>18</sup> and it is not strange that this should produce visceromotor changes as well as the numerous low back pains of the external parietal type (Cases 2, 8, 9 and 10).



FIG. 6. Typical postural deformity in lumbar and lower dorsal area related to lateral pelvic tilt. Genito-urinary disorders and spastic constipation on viscerospinal basis often seen in this type of case. Lighting of figure from one side aids in visualizing abnormalities of skeletal structures.

#### GENITO-URINARY TRACT

In my preliminary report I presented cases in which the viscerospinal syndrome was shown to involve the genito-urinary tract. No detailed description of these cases was given, nor did I attempt to explain the probable physiology. Wills and Atsatt<sup>36</sup> in 1934 offered further substantiating evi-

dence by reporting two patients, one of them (Case 12), in whom ureteral spasm was relieved after postural correction. Complete urological examinations with repeated bougie dilatation of the ureters had proved of little benefit until the extrinsic irritation of the spinal area was removed. This was done along the usual orthopedic lines.

Clinical studies of the urinary tract with the syndrome in mind have been restricted chiefly to ureteral spasm and urinary frequency. Thus far detailed study of renal function or changes in urinary components has not been carried out to a satisfactory conclusion. However, as will be shown, the diuresis of the kidney proper as influenced by the autonomic system may have a direct bearing on the urinary frequency.

To understand the physiological changes involved in the syndrome we must again summarize the autonomic nerve pathways to the kidneys, the ureter and the urinary bladder.

*The Kidneys.* A thick network of sympathetic fibers to the kidney is traced through the major splanchnics and communicating branches from the lesser splanchnics. Vagus (parasympathetic) branches run directly to the renal plexus in most instances passing through the coeliac ganglia. The consensus suggests that the sympathetics govern the urinary output of the kidney principally through vasoconstriction or dilatation of the renal blood vessels.<sup>7</sup> Interesting conjectures arise as to how external somatic factors may influence the renal output. Clinical observations in the past have suggested that exposure with chilling of the lumbar region may be followed by a suppression of kidney output and conversely that hot packs to this region may sometimes stimulate diuresis. If it should prove that a small fraction of renal disorders are due to reflex effects of the viscerospinal type we should be well repaid for the attempt to draw attention to this mechanism.

*The Ureter.* Peristaltic waves in the ureters are probably due to both intrinsic and extrinsic excitation of the thick ureteral musculature.<sup>7</sup> That this peristaltic wave can be so violent as to produce pain is not to be doubted, particularly when a distal portion of the tube is partially blocked. The chief question here arises, however, as to the effect of extrinsic autonomic stimulation in producing the colic. Hryntschak<sup>41</sup> in 1925 corroborated Engelmann's<sup>42</sup> earlier findings that the ureter requires neither intrinsic ganglion cells nor extrinsic nerves for its functional regulation. Kuntz<sup>7</sup> on the other hand is of the opinion that the abundant nerve supply to the ureter cannot be devoid of functional significance. He suggests that "maintenance of the tonus of the ureteral musculature and reflex coördination of the activities of the ureter to contractions of the bladder probably represent the most important functions of the nerves supplying the ureter."

In our series symptoms of ureteral colic, ranging from mild ache in the flank to an extremely severe pain of intermittent type, have been present. How often the antiperistaltic action of a contracting and irritable bladder contributed to the symptomatology is not clear. Ureteral dilatation was found to be of temporary benefit in some instances, but lasting relief was

noted only after a thoraco-lumbar curvature of the spine, or a myositis involving this area was eliminated (Cases 11 and 12).

The best substantiation of the viscerospinal syndrome in relation to the symptoms of ureteral spasm or 'stricture' must come from the urologist. A case studied and reported by Wills is presented.

*Case 11.* Mrs. J. H. P., white, married, 38 years old. She was first seen at the clinic in March 1935.

*Family History:* Father died of a stroke. Mother had "ulcers of stomach." One sister suffered at times from asthma.

*Marital History:* Husband and one child living and well.

*Past History:* Patient had most of the childhood diseases; and tonsillitis and influenza as an adult. A suspension of her uterus was done for lower abdominal pain in 1921. In 1923 during her only pregnancy she developed acute gastric and upper abdominal distress. She was thought to have an intestinal obstruction but no confirmation of this was obtained. In 1925 she fell and injured her "lower spine" which resulted in frequent lumbar pain for some time thereafter. Frequent occipital headaches were a feature of her adult life.

*Present Illness:* The patient's chief complaint on admission was marked distress in the stomach region with occasional nausea. Her symptoms were thought to be worse following meals. She also complained of frequency and of pain radiating down her right posterior thigh. She noted an increase in frequency and also some burning on micturition after being on her feet for several hours. (The latter symptoms had previously been noted under similar circumstances in 1933.) She was moderately constipated. There was a gain of 30 pounds in weight during the past year. She attributed many of her recent symptoms to weakness after an attack of influenza four months prior to this examination.

*Physical Examination:* The patient appeared to be in good health and younger than her recorded age. She was well developed and moderately obese. Her skin was moist and gave evidence of some vasomotor imbalance. Her heart was slightly enlarged to the left. The systolic blood pressure was 110, diastolic 80. The lungs were negative. The abdomen was protuberant and an old lower midline scar was present. No tenderness or hyperesthesia was noted on palpation. Pelvic examination revealed a large, moderately lacerated cervix. The uterus was in the anterior position and pulled to the left. No particular tenderness was elicited by the exploration. On examining the back, areas of tenderness were noted about the third and fourth dorsal spines. A lumbar antero-posterior and lateral curve was found in conjunction with a pelvic tilt to the right. (The latter was apparently due to a shortness of the right leg.)

*Laboratory:* Roentgenographic visualization of the gall-bladder indicated normal function. No stones were visible. (A gastrointestinal series made in Ventura, Calif. a few weeks before was reported to be negative.) Routine blood and urine studies were negative.

*Treatment and Progress:* A program of weight reduction coincidental with postural correction was instituted and a right heel lift was prescribed. Less epigastric distress and "heart burn" was noted within two weeks although some pain persisted in the right hypochondrium for approximately four weeks. The urinary frequency and burning disappeared, however. The patient's condition improved thereafter. She remained free of her symptoms up to April 1936 when her heel lift was not worn for a period of six days. Return to the correction resulted in prompt relief of symptoms.

*Case 12.* A white truck driver, married, aged 26, was referred to us complaining of intermittent pain in the left flank radiating to the back and lower part of the

abdomen. The patient stated that the pain was always worse after he walked or rode in a truck. Usually he felt well on rising, but the pain came on increasingly as the day wore on. Nausea occurred frequently during attacks of pain. He had lost 20 pounds (9.1 kg.). The duration of the condition was two and one-half years in which he had made the rounds of physicians and cultists with no relief.

*Examination:* The examination revealed tenderness high in the left lumbar region and in the lower left quadrant of the abdomen on deep pressure. The abdominal muscles were slightly rigid. The left kidney was not palpable. A cystoscopic examination showed that the mucosa of the bladder was normal. The left ureter was catheterized with difficulty, using a number 4 (French) catheter. The urine gave negative results culturally. No evidence of tuberculosis was seen, and inoculation of guinea pigs gave negative results. Pyelograms showed the kidney to be in normal position; no abnormality was seen. Filling of the renal pelvis reproduced the pain (voluntary statement) but more severe than ordinarily. A diagnosis of stricture of the ureter was made.

*Treatment:* Dilation of the left ureter at first gave relief for a day or so; later these treatments were of no benefit even after dilation with a number 12 catheter. On reëxamination a number 5 catheter was used and met with resistance. Attempts to withdraw it revealed that it was in the grip of a spastic ureter.

The patient was referred to the orthopedic department. Here was found a spastic left dorso-lumbar region with tenderness of the muscles on pressure and a short left leg. There was a moderate scoliosis. The heel was raised one-fourth inch (0.64 cm.), and muscle training was given. The pain left within a few hours and within two weeks the patient could walk several miles without discomfort. The appetite returned and the patient regained five pounds (2.3 kg.) in the first month. Two and one-half months later he was working and free from pain. The only recurrence he has had took place one day when he wore his old shoes on which there was no heel correction.

*The Urinary Bladder.* As does the sigmoid and rectum, the urinary bladder derives its extrinsic nerve supply from the hypogastric (sympathetic) and pelvic (parasympathetic) nerves. This innervation as in many other segmental areas is mutually antagonistic. In general sympathetic stimulation results in inhibition of function whereas the result of parasympathetic stimulation is functional activity of the organ. It is also probable that inhibition of one of the antagonistic nerve groups results in increased effectiveness of the other.

Clinically the same external somatic factors (lumbar myositis, lumbosacral derangements of articulation, etc.) that induce tonic obstipation in the rectum are also of importance in producing motor and sensory disturbances of bladder function. Urinary frequency and urgency, for example, have been noted in many of our cases where lumbosacral irritation was present. Relaxation of the lumbar muscles through physiotherapy or correction of a pelvic tilt has resulted in complete relief of symptoms. (Figure 6.) It is difficult to evaluate the respective rôles of the kidney, ureter and bladder in regard to frequency. In any case the postulates of the syndrome apply to these individually or collectively as shown above. Presumably, on this basis, increased diuresis through the kidney, increased peristaltic action of the ureter, and increased tonic contraction of the urinary bladder acting either singly or together may produce frequency.

## GENERAL DISCUSSION

In reviewing the case reports as a whole and the segmental areas individually there are several points in discussion that are common to the various divisions involved. I have already suggested three points of excitation in or near the spine that act separately or in unison through well defined nerve pathways to produce physiopathological changes in the viscera. I have attempted to demonstrate that these points of stimulation in the skin, the dorsal musculature, and the vertebral articulations (figure 1) may be eliminated or markedly reduced in activity by postural correction and by local physiotherapy. The result of such procedures has been to relieve the patient of symptoms associated with deranged physiological activity in the related segmental areas of the body. To simplify and correlate the various factors in the above relationship in contradistinction to the usual coexistent peripheral radiation phenomena I have suggested the term "viscero-spinal syndrome." This term presupposes that the peripheral and the visceral components of this syndrome may be studied in one or all of the segmental areas. This is borne out by the above studies in spite of the arbitrary grouping of the segments for convenience of description.

In general the type of excitation may be the same at different levels of the vertebral column but the response in the visceral portion of the nerve distribution is entirely dependent upon the characteristics of the viscus involved. In other words ureteral spasm on the viscero-spinal basis may be produced by a myositis of the dorsal musculature (Case 12). Bronchoconstriction may be a result of a similar myositis at a higher level (Cases 3, 4, 5, 6). Ureteral colic on the one hand and asthma on the other are thus related in their pathogenesis but naturally they differ in symptomatology.

It is evident from these studies that the viscero-spinal syndrome is consistent in its manifestations within the range of physiological differences found at different spinal levels. It is not so clear, however, as to the exact rôle of the sympathetic as against the parasympathetic in the production of the syndrome. It is beyond the clinical scope of this paper to determine, for example, whether overstimulation of the sympathetic fibers brings about a pylorospasm of the viscero-spinal type or whether the effect is produced by inhibition of the vagus impulses to the pyloric area. Alvarez<sup>43</sup> has shown in experiments on the rabbit that if intestinal muscle is stimulated while it is in a state of high tone, it may relax, but if stimulated when it is relaxed contraction is likely to result. In man the sympathetic-parasympathetic antagonism described by the physiologists is an imponderable factor when clinical studies such as these are made.

To prove that the points of irritation (cutaneous, muscular or articular) near the spine are primarily stimulating to post-ganglionic fibers supplying the viscus would require more physiological research than is feasible here. It may be that physiopathologic changes in these spinal structures actually produce an inhibition of sympathetic impulses. In turn this inhibition may



allow parasympathetic tone to predominate, resulting in what appears to be an actual parasympathetic rather than sympathetic action on the viscera.

Whatever the correct interpretation of the mode of action may be it is probable that profound physiological changes in the viscera can be demonstrated along the disturbed segmental nerve distributions. Furthermore it is suggested from a study of these cases that continued physiological disturbances may produce definite pathological changes as end-results.

A number of criticisms have been offered by clinicians as to the possible implications of the syndrome. The actual nervous pathways involved were not understood by some. Others denied the postulate of external somatic changes as being related to internal visceral disturbances except through humoral physiology. It has been shown, however, by neuro-anatomists and physiologists that the nerve pathways are present. It has also been shown by the mere mechanical correction of posture—through a heel lift, for example—that an articular defect of the spine may be eliminated and along with it the related visceral disturbance (Cases 1, 10). This would tend to rule out a humoral mechanism.

Following my preliminary report in which I stressed the rôle of spinal curvatures in relation to visceral disturbances the following questions were most frequently asked. "Many people have spinal curvatures and yet do not suffer from visceral disease. Why is the syndrome present in one and not in another?" This is a reasonable question and I believe can best be answered by the orthopedists who are conversant with the external radiation phenomena of radiculitis and intercostal neuritis related to spinal curvatures. Atsatt<sup>18</sup> explains this point as follows: "The neurological complications of scoliosis are governed largely by fatigue and come as the result of lowered skeletal resistance. The forces of gravity continuing to act over a long period of time gradually increase the off center curves, increase the muscle fatigue and irritation and thus give rise to nerve stimulation." He states that "Some incident such as long bed rest, unusual fatigue or strain with muscle atony and atrophy may act as the point of climax to initiate the neurological chain of events."

In untreated cases a history is given of frequent periods during which the patient is free or practically free of his radiation disturbances. The question is asked, naturally enough, "Why should the pain disappear when the scoliosis remains as a focus of irritation?" This again may be answered by the orthopedists who recognize the fact that "intercostal neuritis" may be a recurrent symptom of scoliosis characterized by frequent and often long standing remissions. They explain the vagaries of neuritis, on the basis of changes in muscle tone and fatigue which aggravate a scoliosis and set up articular or muscle irritations. These in turn produce nerve radiation phenomena. It is the *acute* irritation that produces symptoms and not the fixed and stabilized spinal curvature such as found in Pott's disease or in the patient with the congenital hip.

Other factors which are noted in common with the parietal disturbance of the intercostal neuritis type should be discussed at this point. It has been observed that climatic changes of an indefinite nature i.e., from the summer to the fall months or from winter to spring, as well as changes from dry to rainy weather or vice versa, are conducive to attacks in many patients suffering from radiation pain. The visceral component seems to go hand in hand with the peripheral symptomatology in many instances. Interscapular pain, for example, may be accompanied by gaseous distention of the upper abdomen and with epigastric colic. The patient claims in many instances that pain develops when it is "building up for a rain" and is relieved shortly after the rain has fallen. I have no explanation for this but offer the observations for what they are worth. In many cases the symptoms are brought on sharply during the late afternoon as the warmth of the day diminishes. Patients who suffer from the syndrome hesitate to allow themselves to be chilled. They find heat applied to the area of back pain to be of benefit long before such therapy is suggested by the physician.

Still another criticism is directed toward the interpretation of the benefits derived from the mechanical correction involved in these cases. This criticism assumes that the benefits are purely psychic; that something is 'being done' for the patient; that the patient's general health, and therefore his mental state, is improved by a betterment in postural tone. I readily admit that the psychic element is one of the most difficult factors to evaluate in clinical research and that experimental work is often rendered worthless by insufficient consideration of this important element. However, I have little patience with the constant application of the term "psychic benefit" to refute the claims made by clinical investigators in the autonomic field. Undoubtedly the mental state influences the sympathetic and parasympathetic balance in many of the patients studied. It is also true that psychotherapy and sedation have aided in the recovery of patients with visceromotor symptoms. But these factors have been repeatedly eliminated as being of minor importance in a given case once the viscerospinal syndrome is definitely established. In questionable instances local anesthesia of the related cutaneous areas according to the technic of Weiss and Davis<sup>33</sup> has been used to rule out the psychalgias. Preliminary sedation as well as placebos have also been used in making the differential diagnosis and in directing the patient's attention away from the real therapeutic procedures. As a matter of fact the difficulty has often been to persuade the patient that such a small item as a heel correction, or simple exercises for a scoliosis has any connection with his cure. Many times a placebo has been used to keep a patient satisfied and to insure his return for observation because of his skepticism in regard to his "unrelated" treatment. I believe that patients in this group are the least liable to be benefited because of subjective considerations. Their typical reaction is expressed by the common question, "Doctor, why do you pay so much attention to my back, when it's my stomach that is hurting me?"

In closing may I reiterate the necessity for recognizing the importance of physiology in relation to clinical problems. Viewing disease from the pathological approach is often a confession of failure to recognize the early physiological changes. Surgery, for example, has taken the lead in a field of physiology which should rightfully belong to the internist. The essential hypertensive, long considered a pet of the internist, is referred to the surgeon for splanchnic section. To relieve the patient with cardiac pain it is the surgeon who is asked to inject the upper thoracic ganglia. Raynaud's disease is often given up as intractable by the internist and sympathectomies are performed. But with all his success the surgeon admits he is merely severing efferent or afferent pathways which act as simple conduits for physiological impulses. He is not attacking the basic condition which primarily initiates these impulses. There is a derangement yet more remote than the ganglionic fibers involved in the cardiospasm or the hypertonicity of the intestinal tract. In cases presenting the viscerospinal syndrome the basic stimulus (or inhibition) is superficial to the cord and consists of afferent impulses. From our studies an important etiological factor is the somatic triad: Skin, dorsal musculature or vertebral articulations (figure 1). By correcting disturbances in this triad we may find at least one substitute for the hitherto necessary attack by the surgeon on the visceral nerve pathways anterior to the spine. Here we are dealing with causes rather than with end results of autonomic nerve disorders.

The body must be integrated as a whole. It must function as a whole adapting itself to external as well as internal stimuli. For some time the clinician has been so engrossed in the effects of visceral dysfunctions and their *outward* manifestations that he has neglected the skeletal structures with their disturbance reflected *inward* on the viscera. The syndrome herein described emphasizes the latter phase of physiological balance.

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# CALCAREOUS AORTIC STENOSIS; REPORT OF NINE CASES WITH AUTOPSY FINDINGS \*

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CALCAREOUS aortic stenosis, or stenosis of the aortic valve with calcification of the cusps, is a clinical entity which is receiving increasing attention. Probably the most important clinical feature has been, and remains, the disproportion between the clinical signs and symptoms during life as compared with the marked changes present in postmortem examination. Patients suffering from aortic stenosis have a clinical course which is entirely distinctive from that of either mitral disease or mitral and aortic disease combined. On analyzing the age incidence, the physical signs, the age at which symptoms first appear and the mode of death, it becomes quite evident that patients with calcareous aortic stenosis comprise a well segregated and defined group. A rather distinctive and characteristic finding in this group is the paucity of symptoms directing attention to the heart until the abrupt onset of cardiac manifestations.

## LITERATURE

Trousseau<sup>1</sup> was among the earliest clinicians to recognize the peculiarities associated with aortic valve disease. He called attention to the occurrence of sudden death in lesions of this valve and "the absence of the assemblage of the phenomena which constitute the general symptoms of disease of the heart." In 1892, Vaquez,<sup>2</sup> with his teacher Potain, examined a woman, 60 years of age, who had a murmur of aortic stenosis. Some 20 years later he again saw her on her death bed, and learned that in the interval of 20 years she had been very comfortable.

Osler<sup>3</sup> borrowed a phrase from Oliver Wendel Holmes when he expressed the thought that this lesion is not only compatible with continued good health, but that "it may promote longevity." Following Osler's discussion in 1888, contributions by Cabot,<sup>4</sup> Moenckeberg,<sup>5</sup> Christian,<sup>6</sup> Clawson and his co-workers,<sup>7</sup> Hathaway,<sup>8</sup> Libman,<sup>9</sup> and more recently Margolis and his co-workers,<sup>10</sup> McGinn and White,<sup>11</sup> and others have added a great deal to the present knowledge of calcareous aortic stenosis.

In this communication we are reporting nine cases of this clinical entity with a summary of the essential findings of the cardiovascular system as noted at autopsy. All of our cases but one were males. The ages ranged between 46 years and 84 years.

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## CASE REPORTS

*Case 1.* A. K., a male adult, aged 72 years, was admitted to the hospital on April 23, 1935, complaining of dyspnea and orthopnea of two months' duration. The family history and the past history were essentially negative. The present illness dated to some eight weeks before admission when the patient first began to complain of shortness of breath on exertion and the necessity of sleeping "sitting up in bed." Prior to admission to the hospital he had been under digitalis therapy and had occasional precordial pain lasting for a few minutes at a time. The essential findings on physical examination were dyspnea, orthopnea and cyanosis in a well preserved, white, male adult. The heart was enlarged to the left, the rhythm was regular, and the sounds were of poor quality. At the lower end of the sternum and somewhat to the left, a saw-rasping systolic murmur was heard. Over the aortic area a rough systolic murmur was heard which radiated upward into the vessels of the neck. The second aortic sound was not audible. Râles were heard at the right base, and the liver extended some 6 cm. below the costal border. There was no peripheral edema. The systolic blood pressure was 100 mm. of mercury and the diastolic 48 mm., and the pulse rate was 60 per minute. Serology was negative. Blood chemistry findings were normal. There was increasing dyspnea and orthopnea. The patient died 12 hours after admission to the hospital.

*Autopsy Protocol.* The heart weighed 580 grams and was markedly hypertrophied and dilated. The wall of the left ventricle measured 2 cm. in thickness, that of the right 0.5 cm. in thickness. All the chambers of the heart were markedly dilated and contained postmortem clots. The tricuspid valves were slightly thickened and opaque. The chordae tendineae were slightly hypertrophied. A probe, passed from the left ventricle into the aorta, met with marked obstruction and was admitted into the aorta only with difficulty. The semilunar aortic valves were thickened, markedly sclerosed and calcified. The edge of one of the cusps measured 0.5 cm. in thickness and was markedly calcified. The pulmonary valves were slightly sclerosed. The coronary arteries were pipe-stem in nature, markedly sclerosed and easily traced throughout their entire course. There was no recent obstruction. The aorta showed marked atheromatosis, calcareous deposits and ulcerations.

*Comment.* This 72-year-old man was clinically well until two months prior to his death. Following the onset of symptoms of heart failure there was a rapid and progressive downhill course. The important findings on examination of the heart were the rough systolic murmurs heard over the aortic area and in the region of the mitral valve, and an inaudible second aortic sound. At autopsy the aortic valves were found to be thick, sclerosed and calcified.

*Case 2.* S. G., a white male adult of 46 years of age, was first admitted to the hospital on April 8, 1935, complaining of a cough of many years' duration and shortness of breath of one month's duration. The patient's mother had died of "heart trouble" but there was no other family history of cardiovascular disease. The past history revealed the fact that at the age of 12 he had had malaria, at 18 had a nephropexy, at 30 had gonorrhea, and at 39 had pneumonia and pleurisy. There was also a past history of frequent upper respiratory infections. One year prior to admission to the hospital he had been having increasing shortness of breath on exertion and for the past month had had attacks of nocturnal dyspnea and palpitation. The essential findings on examination were dyspnea and orthopnea, enlargement of the heart to the left, presence of a presystolic murmur at the apex, and a rough systolic murmur over the aortic area, transmitted upward to the vessels of the neck. The second aortic

sound was not heard. A thrill was felt over the aortic area. The peripheral blood vessels were thickened and the pulse was small. Cardiac rate was rapid, rhythm was regular and the muscle tone was of fairly good quality. There was evidence of right and left hydrothorax and the liver was enlarged two fingers-breadth below the costal border. No sacral or pretibial edema. Roentgen-ray examination showed an enlargement of the heart, predominantly left ventricular, with increased vascularity throughout the pulmonary parenchyma and effusion in both chests. Fluoroscopic examination, with the administration of barium outlining the esophagus, revealed a left auricular bulge and enlargement of the left ventricle. Electrocardiographic studies showed: Lead I, regular sinus rhythm, slurring of R and negative T. Lead II, negative P, slurred R, depressed ST and diphasic T. Lead III, negative P, slurred and notched QRS. Interpretation: Left axis deviation, severe myocardial disease and auricular involvement. The blood pressure varied from 140 to 118 systolic and from 84 to 60 diastolic. Blood chemistry findings were normal, and examination of the urine showed a trace of albumin and a few granular casts. Following the continuance of bed rest, low caloric diet and digitalis therapy, signs of congestive heart failure gradually decreased and the renal findings returned to normal. The pleural effusion disappeared, the patient's condition improved, and he was discharged on April 23, 1935, 15 days after admission. The diagnosis at this time was: arteriosclerotic heart disease with calcareous aortic stenosis, calcification of the mitral ring, left and right heart failure and bilateral hydrothorax. Four days after discharge from the hospital the patient was readmitted with a history of having experienced a very severe attack of pain in the epigastrium several hours previously. The pain continued, radiated to both axillae and shoulders, and the patient "felt as if dying." Examination showed the patient to be dyspneic and cyanotic; the heart sounds were weak and rapid and the skin cold and clammy. Blood pressure on admission was 128 systolic and 60 diastolic and within a few hours dropped to 98 systolic and 64 diastolic. The murmurs heard and described on the first admission were present but less intense in character. Within 24 hours the temperature was elevated to 102° F. A pericardial friction rub was heard over the lower end of the sternum. Electrocardiographic study at this time showed changes indicative of progressive myocardial damage as compared with the tracing taken some three weeks previously, but no characteristic changes to indicate a recent coronary occlusion. His condition remained critical. Eight days after admission he suddenly became markedly dyspneic and cyanotic. The pulse was rapid and feeble and the blood pressure was so low it could not be estimated. The chest was full of râles, and the patient expired within a few minutes after the onset of this attack.

*Autopsy Protocol.* The heart and aorta weighed 500 grams and lay free in the pericardial sac. On the anterior surface of the left ventricle, close to the apex, there was a small circumscribed patch of fresh fibrin. The left ventricle was hypertrophied and there was very little dilatation present. The aortic valve was rigid and fixed and the leaflets were replaced by firm bone-like masses. The anterior descending branch of the left coronary artery presented in its lumen a fresh adherent thrombus about one and one half centimeters from its termination. The myocardium in this vicinity showed hemorrhagic infarct.

*Comment.* The marked calcification of the aortic valves, as noted in the autopsy, undoubtedly existed many years before the onset of the clinical symptoms of heart disease which were first manifested two years prior to death. The anginal syndrome, we believe, was due to the coronary artery disease. This man was the youngest of those included in this group. The classical attacks of left ventricular failure were followed by coronary artery thrombosis which necessitated re-hospitalization. The physical examination



revealed criteria which we believe are confined to those who have calcareous aortic stenosis, namely a rough systolic murmur over the aortic area transmitted to the vessels of the neck, absent aortic second sound, palpable thrill over the aortic area and small pulse.

*Case 3.* N. W., a male adult 66 years of age, was admitted on April 10, 1934, with a history of five previous attacks of precordial pain and shortness of breath during the preceding six months. His immediate condition, necessitating hospitalization, was of 12 hours' duration, and was manifested by precordial pain, vice-like in character, and by dyspnea and cyanosis. The essential findings on physical examination were the marked cyanosis of the lips, ears and finger-tips, pulmonary edema, systolic murmur and thrill over the aortic area, and a decrease in aortic second sound. An electrocardiogram taken at this time revealed left axis deviation and severe myocardial damage. Response to treatment for the attack of left ventricular failure by sedation, bed rest and digitalis therapy was satisfactory. The patient improved and was discharged from the hospital four weeks after admission. He was comparatively well for some 22 months when he was readmitted to the hospital (February 27, 1936), with a history of increasing dyspnea and precordial discomfort. These symptoms had appeared approximately a week prior to admission and were initiated by an attack of breathlessness which woke him from his sleep during the night. On examination there were all the evidences of left ventricular failure (numerous râles throughout both lung fields, marked pallor and cyanosis of the finger-nails and dyspnea). The essential findings on examination at this time were: the high-pitched musical murmur heard at the apex and transmitted upward to the aortic region where it was accentuated, absence of the aortic second sound, and enlargement of the liver (two fingers-breadth below the costal border). The systolic blood pressure was 210 and the diastolic 100 mm. Treatment by dry phlebotomy and sedation brought about definite relief of orthopnea, and the moisture in the lungs disappeared. An electrocardiographic study showed marked left axis deviation with progression of the severe myocardial damage, as compared with the electrocardiographic study taken in 1934. Some 24 hours after admission, when the patient was having his breakfast, he suddenly fell over dead.

*Autopsy Protocol.* The heart and aorta weighed 600 grams. The left ventricle measured 1.3 cm. in thickness and there was flattening of the musculature. The aortic valve showed marked calcification and the mitral valve revealed thickening of the cusps but no calcification. The intima of the aorta was brittle and calcified. The coronary orifices and vessels were patent throughout and revealed no evidence of old or recent thrombosis.

*Comment.* The postmortem examination of the heart failed to indicate any evidence to explain this rather sudden and unexpected death. The possible mechanisms responsible for the sudden death are discussed later.

*Case 4.* W. C., a white male adult, 80 years of age, was first admitted to the hospital, February 18, 1936. For three years prior to admission he had been complaining of "pain over the heart and in the back, with shortness of breath, getting worse in the last three months, and swelling of the legs for one month." He was able to carry on his work until some two (2) months prior to admission when, because of breathlessness and pain over the heart, he had to discontinue all activity. In recent months he was compelled to sit upright in order to sleep. On the evening of admission to the hospital he complained of "sharp pain over the heart with loss of breath." The essential findings on physical examination were the enlargement of the heart (apex beat in the sixth interspace at the anterior axillary line), a sharp, rasping, high-pitched

murmur at the apex, replacing the first sound, intensification of this systolic murmur at the aortic area, diminished aortic second sound and systolic thrill over the aortic region. Moist râles were heard at both bases. The liver was slightly enlarged and tender, and there was a slight pretibial edema. Blood pressure 140 systolic, 100 diastolic. The diagnosis of calcareous aortic stenosis with extension of the calcification downward to the mitral valve was made. After several days the patient left the hospital against advice, only to return three months later with marked dyspnea, orthopnea and precordial distress, palpitation and moderate edema of both legs. He presented the signs of congestive heart failure. On examination of the heart, the rasping murmurs previously described were heard over the mitral and aortic areas. Electrocardiographic studies done on three occasions showed auricular fibrillation with left bundle branch block. The patient failed to respond to treatment and died one month after admission to the hospital.

*Autopsy Protocol.* The heart weighed 700 grams and showed predominant enlargement of the left ventricle. Externally over the left ventricle there was a medium-sized, white, calcified, adherent plaque. On section the left auricle was average in thickness and the mitral valve leaflets were markedly calcified. The mitral orifice admitted one and one-half fingers. The left ventricle was markedly hypertrophied. The aortic valve leaflets were extensively calcified and opaque. The coronary arteries showed extensive calcification and sclerosis throughout, but there were no occlusions. The aorta showed marked atherosclerosis and calcified areas throughout. There was an aneurysm present in the hepatic artery, close to its origin, which was 1.5 cm. in diameter and filled with an old laminated blood clot. The spleen weighed 200 grams, was slate blue, and showed areas of old infarction. The kidneys showed old wedge-shaped areas of scar tissue.

*Comment.* The finding of a healed aneurysm of the hepatic artery and the presence of the infarcts in the spleen and kidneys naturally raise the question as to whether or not this man at some time previously had had a subacute bacterial endocarditis which had healed.

*Case 5.* P. G., a white male adult, 55 years of age, was admitted to the hospital in coma, on November 14, 1933, and died within a few hours. The history obtained from a relative indicated that the patient had had a known hypertension for three years, and that three weeks prior to admission he had sustained an injury to the left index finger. There was no history of symptoms suggestive of progressive heart failure. The "patient collapsed and went into coma" and was brought to the hospital. The physical examination revealed a comatose white male adult with extreme cyanosis. The heart was enlarged, rate increased, and rhythm regular. A loud rough systolic murmur was heard over the apex and the aortic area. The aortic second sound was distinctly less prominent than the pulmonic second sound. The lungs were clear; the liver was enlarged to two fingers' breadth below the costal border. There was no edema of the sacrum or of the tibia. There was an infection of the left index finger with pus exuding from several incisions. In view of the comatose state, spinal tap was done and the fluid returned was bloody but under normal pressure. There was no sugar present in the urine.

*Autopsy Protocol.* Examination of the brain revealed the fourth ventricle to be distended by a blood clot. On serial section, this blood clot extended throughout the entire fourth ventricle and seeped into the central canal of the cord, and the pons showed several hemorrhages throughout its length. There was no evidence of congenital aneurysm of the cerebral vessels. The heart weighed 800 grams. The lumen of the right ventricle was encroached upon by the bulging of the septum inward. The mitral orifice admitted two fingers. The valve leaflets were transparent and shiny.

The lumen of the left ventricle was of average size and the musculae carnae were rounded. The wall of the ventricle measured 1.8 cm. and was of a homogeneous brick-red color. The aortic valve had a bicuspid arrangement. The leaflets were shortened and the edges were somewhat rounded and calcified. The coronary orifices were widely open and the branches of both the right and left coronary arteries showed a moderate arteriosclerotic process. There was no sclerosis of any of the vessels, nor was there a recent thrombosis. The aorta showed a moderate atheromatous process without calcification.

*Comment.* Death in this case was due to extensive hemorrhage into the fourth ventricle of the brain. To the best of our knowledge there were no symptoms associated with the cardiac abnormalities as noted in postmortem examination. At autopsy a congenital bicuspid aortic valve was found with extensive calcification of the ring and leaflets. Examination of the cerebral blood vessels did not disclose any congenital or mycotic aneurysm.

*Case 6.* S. F., a white male adult, 47 years of age, was admitted to the hospital on October 15, 1936, and died within a few hours after admission. He had been well until midnight prior to the day of admission when he suddenly developed dyspnea and orthopnea. On admission to the hospital he was markedly cyanotic and expectorating a frothy, bloody sputum. Examination showed both lungs full of bubbling râles. It was difficult to hear the heart sounds because of the pulmonary edema. The blood pressure was 160 systolic and 96 diastolic and dropped to 130/90 following phlebotomy of 300 c.c. There was slight improvement following this procedure. The cardiac rhythm at this time was found to be totally irregular. Muscle tone was poor and there was no accentuation of the aortic second sound. It was difficult to evaluate the question of cardiac murmurs because of the pulmonary edema.

*Autopsy Protocol.* The heart weighed 500 grams. The mitral orifice admitted the tip of the index finger. On section the posterior and lateral wall of the left auricle was covered with a large, friable, grayish-brown, laminated thrombus which was firmly adherent to the auricular wall and when pulled away left an irregular granular surface. The mitral valve was grayish-white in color, opaque and rigid, and in several areas calcified. The chordae tendineae were markedly thickened, reduced in number, pearly-gray in color and shortened. The aortic semilunar valves were likewise grayish-white in color and rigid. There were adhesions between the cusps, with definite encroachment upon the lumen. The cusps adjacent to the right coronary orifice showed calcification. The septum membranaceum was grayish-white in color and semirigid. The section of the ventricle showed the musculature to be brick-red. Both right and left coronary arteries showed patent orifices with moderate diffuse atheromatosis distributed throughout their major branches. The aorta showed moderate diffuse atheromatosis which was slightly more marked at the lower end of the abdominal portion.

*Comment.* This patient had no known previous history of rheumatic fever and had no manifestations of disease until a few hours prior to admission to the hospital, when he suddenly developed acute symptoms of cardiac failure and went rapidly downhill despite all therapy. Atherosclerotic changes in the coronary arteries and aorta were rather mild. The extensive calcific changes were limited to the aortic and mitral valves and their respective rings. The extensive changes in the chordae tendineae and the papillary muscles are highly suggestive of previous rheumatic infection.

*Case 7.* W. L., a white male adult of 84 years, was admitted to the hospital on January 31, 1936, with a history of increasing dyspnea, ankle edema and nocturia of five months' duration. For five days prior to admission he complained of "very marked weakness." The essential findings on physical examination were the numerous râles throughout both lung fields, decrease in intensity of all heart sounds, absence of apical impulse, pulse rate of 40, moderate degree of ankle edema and a blood pressure of 140 systolic and 70 diastolic. Electrocardiographic study showed a complete heart block with auriculo-ventricular dissociation. The patient lapsed into coma soon after arrival at the hospital, developed Cheyne-Stokes respiration and died 50 hours after admission.

*Autopsy Protocol.* The heart weighed 575 grams. The left ventricular wall was hypertrophied and dilated, measuring 1.8 cm. in thickness. Multiple areas of fibrosis were present in both ventricular walls. The aortic valve was rigid and diffusely calcified. There was an old thrombus formation in the right coronary artery, 5 cm. from its origin. The left coronary artery and branches were patent. There were small areas of fibrosis in the interventricular septum.

*Comment.* The fibrosis in the interventricular septum was probably due to extension of calcific changes from the aortic valve and ring. This fibrosis in the interventricular septum, we believe, was responsible for the changes in the cardiac rhythm (auriculo-ventricular dissociation, with complete heart block).

*Case 8.* E. N., a white female adult, 74 years of age, was admitted to the hospital on March 1, 1932, with a history of "heart trouble for the past six months." There was progressive shortness of breath and increasing edema of the lower extremities. She had been taking tincture of digitalis before admission to the hospital. Three days prior to hospitalization she became semistuporous. On admission to the hospital she was found to be in stupor, markedly dyspneic and cyanotic. The heart was enlarged to the left. The apex was in the sixth interspace, outside the nipple line. The sounds were totally irregular with a marked rough systolic murmur heard over the entire precordium. There were râles at both bases. The liver was enlarged to two fingers-breadth below the costal border and the edema of both lower extremities extended upward almost to the groin. Patient died within 12 hours after admission to the hospital, without rousing from coma.

*Autopsy Protocol.* There was marked thickening of the left ventricle which bulged into the lumen of the right ventricle. The mitral orifice admitted only one finger. The aortic semilunar valve was markedly sclerotic and in the anterior cusp there was a calcified nodule about 1 cm. by 0.5 cm. Both coronary arteries were patent. The descending thoracic aorta showed calcified plaques about one-half inch to one inch in length.

*Comment.* This patient had suggestive evidence, on postmortem examination, of a healed rheumatic mitral valvular disease (stenosis). There was a six months' history indicative of congestive heart failure. The calcification present was confined to the aortic valve leaflet.

*Case 9.* J. S., a white male adult, aged 65 years, was first admitted to the hospital in 1934, for gastric distress following meals. At this time a loud systolic musical murmur was heard over the entire precordium, especially intense over the aortic area and transmitted to the vessels of the neck. The second sound at the aortic area was diminished in intensity. Roentgen-ray study revealed cardiac enlargement and sclerosis of the aorta. His stay at the hospital was uneventful and he left against

advice. Two years later, in 1936, he was readmitted because of increasing dyspnea, orthopnea and nosebleeds. The blood pressure at this time was 170 systolic and 105 diastolic, and the cardiac findings were essentially the same as those noted previously. There were numerous râles at both bases, and the pulse rate on admission was increased (rate 120). Electrocardiographic study showed a marked degree of left axis deviation with evidence of myocardial damage. Digitalis therapy and rest in bed brought about a striking improvement and the patient left the hospital five days after admission, much improved. He was readmitted to the hospital for the third time on January 5, 1937, some six months following previous discharge. Marked dyspnea and orthopnea, aggravated by a recent upper respiratory infection, brought him to the hospital. At this time there was evidence of congestive heart failure as manifested by numerous râles in both bases, fluid in the right chest, enlargement of the liver, fluid in the peritoneal cavity and edema of the ankles. The heart was definitely increased in size and a rough systolic murmur, most intense over the aortic region, was heard over the entire precordium, and was transmitted upward into the vessels of the neck. There was a systolic thrill over the aortic area. The second aortic sound was absent. Digitalis therapy and sedation failed to bring about any improvement and there was gradual increase in the signs of heart failure. The patient died two weeks after admission.

*Autopsy Protocol.* The heart weighed 600 grams. The visceral pericardium was adherent to the parietal pericardium at one point on the anterior surface of the left ventricle. Over the entire apex and over the septum there were irregular grayish-white areas immediately beneath the mural endocardium. At a point one-third down on the septum the left ventricle showed a sudden transition from the normal mural endocardium to a raised, firm, grayish-white lining. The wall of the ventricle thinned out as the apex was approached (thickness of 4 mm.). The entire apex was ballooned and filled with an irregular laminated thrombus. The aortic semilunar valves were rigid, opaque, and showed numerous raised areas bright yellow in color, some of which were bony hard in consistency. The area between the left anterior cusp and the anterior mitral flap showed a similar calcification. The base of the aorta showed diffuse atheromatosis with calcification. The coronary orifices were both patent. The anterior branch of the left descending coronary artery was completely occluded from a point 3 cm. from its origin and for a distance of 1.5 cm. This length of the artery contained a thick, completely occluding calcific node. Distal to that point, the vessel was of average appearance. The circumflex branch of the left coronary artery showed a moderate sclerosis. The right coronary artery was likewise completely occluded at a point 6 cm. from its origin and for a distance of 1 cm.

*Comment.* This patient had hypertensive heart disease with extensive sclerotic changes in the coronary arteries with evidences of old and recent occlusion. The extensive calcification of the aortic valves undoubtedly contributed in some degree to the increasing cardiac insufficiency. The clinical course in this case was primarily influenced by the changes in the coronary system.

#### ETIOLOGICAL FACTORS

The causes of calcareous aortic stenosis are commonly ascribed to :

1. Degenerative changes incident to atherosclerosis.
2. Rheumatic fever.
3. Healed infective endocarditis.
4. Changes superimposed upon a congenital defect of the aortic valves.

1. *Atherosclerosis*. In 1672 Rayger<sup>12</sup> first described calcification of the aortic valves. A detailed pathological description was first given by Moenckeberg<sup>5</sup> in 1904. He described in detail the pathogenesis and morphology of aortic stenosis with calcareous deposition. This author called attention to the fact that lesions of an atherosclerotic nature affecting the valves regularly begin to appear beyond the age of 35 years. In the atherosclerotic group, Moenckeberg<sup>5</sup> described an "ascending valve sclerosis" wherein the changes take place in the layers of the valve facing the sinus of Valsalva, from which point the process extends up the valve leaflet to the free margin. He also described a "descending type" where the lesion starts primarily in the aorta and extends down onto the valve leaflet and commissures. The fact that calcareous aortic stenosis is seen most frequently beyond the age of 50 would indicate that the most common cause of these changes is atherosclerosis. However, even when there are most advanced calcific deposits in the aortic valves with concomitant lesions in the aorta or coronary arteries or both a non-infective basis of the disease cannot be assumed. The difficulty in evaluating the question of atherosclerosis or infection as factors has been well stressed by Hathaway<sup>8</sup> in his summary of 52 cases.

2. *Rheumatic Fever*. The fact that calcareous aortic stenosis is seen in the age group in which active endocarditis seldom occurs would make it appear that degenerative heart disease and the atherosclerotic changes associated with the degenerative processes are the most frequent causes of calcific changes in the aortic valves. The difficulty in obtaining any definite history of rheumatic infection in many cases also favors this concept. It is proper to call attention to the fact that, since this group is farthest removed from that period of life during which active rheumatic fever is common, evidences of active rheumatic disease are not to be expected either on clinical examination or at postmortem examination. The failure to elicit a history of previous rheumatic disease is not unusual, for even in mitral stenosis, which is almost always due to rheumatic fever, a history of such infection is obtained only in about 50 per cent of the cases according to the analysis of Christian.<sup>6</sup> In an excellent survey of 123 cases of aortic stenosis McGinn and White<sup>11</sup> report a previous history of rheumatic fever in one-third of the entire group. There was a definite history of rheumatic infection in 23 per cent of those who came to autopsy and in 46 per cent of the clinical series. Cabot<sup>4</sup> concluded that his cases were due to previous rheumatic disease but could not very well correlate the age and sex incidence with rheumatic fever. In none of our cases was there any history suggestive of previous rheumatic infection. In Cases 2 and 8 of our series the probability of previous rheumatic disease must be considered even though there were concomitant evidences of degenerative changes.

3. *Healed Infective Endocarditis*. We are indebted to Libman<sup>9, 23</sup> for our knowledge concerning the relationship of healed subacute bacterial endo-

carditis to chronic valvular defects. According to Libman's<sup>28</sup> concept healing of the valve takes place after the patients become bacteria-free. Subsequently, calcific masses are deposited in the valves which interfere with their function. In these cases there is usually a history of a primary valve infection complicating the rheumatic phase. This is followed by a free interval of months or years with subsequent reinfection of the diseased valve, commonly by the *Streptococcus viridans*. The clinical course at this stage may be that of a severe active bacteremia, or the infection may be very low grade and run a protracted clinical course. If healing takes place there may be evidence only of a valvular defect. Case 4 of our series presented the following pathological feature which leads us to believe that it belongs in this group of healed infective endocarditis. This patient had an aneurysm of the hepatic artery and areas of infarction in the kidney and in the spleen, in addition to the calcification of the aortic and mitral valves. The opinion that bacterial endocarditis may be healed by calcification was recently expressed by Perry.<sup>13</sup> This author states that it is probable that in those cases where calcific nodes are found on one of the cusps of the aortic valve, in the absence of atheromatosis, an unrecognized active bacterial endocarditis later healed may have been the cause. The presence of old renal infarcts, the absence of pericardial adhesions, and the fact that both diseases (calcareous aortic stenosis and subacute bacterial endocarditis) predominate in males, are, in the opinion of Cabot,<sup>4</sup> suggestive evidence of healed subacute bacterial endocarditis.

4. *Congenital Defects.* We are greatly indebted to Osler<sup>14</sup> for the present day knowledge of the relationship between a congenital defect (bicuspid aortic valve) and the development of calcareous aortic stenosis. The predisposition of this type of congenital lesion to calcific deposition or the occurrence of superimposed infection was shown by Osler and by Abbott.<sup>15</sup> In Case 5 of our series we have all the criteria as laid down by Osler for the identification of congenital bicuspid valve. We believe that the deposition of calcium in this case was engrafted upon a congenitally defective valve in which infection did not occur. Careful search of other organs and viscera failed to reveal any presumptive evidence of a previous endocarditis. Recent analysis of nine cases<sup>16</sup> of congenital bicuspid aortic valve indicate the marked tendency for calcific deposition in these individuals. In our patient there were no other congenital abnormalities either in the cardiovascular system or elsewhere, other than in the bicuspid aortic valve. Syphilitic changes in the aorta with the subsequent pathological changes involving the aortic valves never result in a stenotic lesion of this valve.

### CLINICAL FEATURES

The murmur of calcareous aortic stenosis may be described as extremely loud and may be either musical or hard and saw-rasping. At times this murmur may be so loud that it may be heard; to quote Stokes,<sup>17</sup> "at some

distance and with a patient resting in a chair, the thrill may be transmitted to the arms of the chair." The radiation of the murmur is classical. Invariably the direction is upward and to the right side of the neck, and at times the murmur may be heard in the paravertebral area on the right side posteriorly at the level of the second thoracic vertebra. If there is associated calcification of the mitral ring there may be a loud systolic murmur heard at the apex.<sup>22</sup> This murmur radiates upward along the left sternal border and, as described by Libman,<sup>22</sup> becomes intensified over the aortic area. The apical murmur under these circumstances is also transmitted to the left axilla.

A distinct thrill over the aortic area is usually present in calcareous aortic stenosis. The thrill at times is more perceptible when the patient is in the upright position. The character of the second aortic sound is an important consideration in the diagnosis. The absence of the second sound or a marked diminution in its intensity is the most important single confirmatory sign in calcareous aortic stenosis. This is especially true if hypertension exists. At times the second sound is replaced by a soft blowing diastolic murmur. In our studies we have not encountered any signs of clinical insufficiency of the aortic valve.

The advanced age of the average patient is such that changes in the wall of the radial artery make the detection of fine differences in pulse excursion rather difficult. We, therefore, did not place much importance on the presence of the typical pulse of aortic stenosis (*rarus, parvus, tardus* and *longus*). Information gained from the study of the blood pressure values was not significant for the reason that this factor is dependent on too many variables (insufficiency of the left ventricle, myocardial tone, condition of the peripheral vessels, etc.).

Angina as a prominent symptom in calcareous aortic stenosis has recently been reported by Boas.<sup>18</sup> This author stressed not only the symptom of precordial pain but also called attention to heart-block and a tendency to syncope in this group. In view of the high incidence of associated calcification of the coronary arteries with some resultant insufficiency, it is not surprising that angina pectoris is a frequent clinical feature. Pain has been known to be accompanied by sudden death, with or without changes in the rhythm. When the changes in the annulus fibrosus extend into the membranous portion of the septum, changes in cardiac rhythm are to be expected. Partial or complete block or bundle branch block may follow if this septal process takes place in the angle between the anterior cusp and the right posterior cusp, at which site the conduction tissue is located.<sup>19</sup> In a patient who had calcareous aortic stenosis with attacks of syncope, Marvin and Sullivan<sup>20</sup> obtained electrocardiographic tracings during the period of syncope. They concluded that these attacks of syncope were due to an abnormal carotid sinus reflex. This is of practical clinical importance especially in undertaking an operation upon an elderly patient who shows signs of calcareous



aortic stenosis. Sudden death while under anesthesia may be due in these patients to an abnormal carotid sinus reflex or rhythm changes. Sudden death in Case 3 (N. W.) could not be explained by any morphological changes. A mechanism such as that described by the above authors might be invoked in this death. The sudden deaths which occurred in Cases 2 and 9 were due either to acute coronary artery occlusion or to extension of the calcification from the aorta to the coronary arteries.

### SUMMARY

Calcareous aortic stenosis is a disease predominantly affecting males and usually occurring past middle life, but occasionally encountered in younger persons. The outstanding physical signs are the typical murmur, accompanied by a diminished second aortic sound and a palpable thrill over the aortic area. The heart is enlarged. The stenotic aortic lesion is usually accompanied by changes (atheromatous) in the aorta and coronary arteries and at times by calcific changes in the mitral valve and ring. The syndrome of angina pectoris and disturbances in cardiac rhythm are commonly seen in this disease. The occurrence of sudden death is a striking and frequent characteristic.

In this communication we have reported nine cases of calcareous aortic stenosis and have discussed the etiological factors, morphological changes and clinical features.

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# THE DETERMINATION OF BILIARY TRACT INFECTION WITH THE ENCAPSULATED DUODENAL TUBE\*

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THAT it is now possible to determine biliary tract infection with considerable accuracy, without operation, has been proved by the correlated pre-operative and operative bacteriological findings in a series of 120 patients with chronic biliary tract disease. In each case a pre-operative duodenal drainage was performed under sterile precautions with the encapsulated Twiss duodenal tube,<sup>1</sup> and the bacteriological findings of the duodenal bile were compared with those of specimens obtained from the biliary tract at operation. The findings were identical in such a large proportion of the cases studied that the use of this procedure as a diagnostic measure seems fully justified.

The importance of being able to ascertain infection of the biliary tract cannot be overestimated. The excellent results of early surgery in patients with infection are well known, likewise in those with stone, obstruction, or malignancy. On the other hand, careful follow-up studies have shown that in the absence of these conditions, surgical treatment frequently gives unsatisfactory results. We believe that this can be attributed in many cases to an inability to determine the presence pre-operatively of biliary tract infection. Another reason is disregard for functional disorders or dyskinesias of the biliary tract, usually not associated with infection, which were first described by Westphal<sup>2</sup> and by Ivy and Sandbloom.<sup>3</sup>

In biliary tract disease reliable evidence of infection can be obtained only by isolation of pathogenic bacteria upon culture. This is possible by the use of the duodenal tube, which was introduced by Gross<sup>4</sup> and Einhorn,<sup>5</sup> and greatly improved in diagnostic value by the Lyon<sup>6</sup> method of duodenal intubation. Further contributions have been made by Rehfuss,<sup>7</sup> Levine,<sup>8</sup> and many others. The reliability of diagnostic duodenal drainage is dependent upon a recognition of the fact that the normal fasting duodenum is sterile, as established by the investigations of Cushing and Livengood,<sup>9</sup> MacNeal and Chace,<sup>10</sup> and Kellogg.<sup>11</sup> The value of cultures taken under proper precautions in establishing a diagnosis of biliary tract infection has been recognized for many years; among early contributors to the literature should be mentioned Lyon,<sup>6</sup> MacNeal and Chace,<sup>10</sup> Smithies,<sup>12</sup> Whipple,<sup>13</sup> and Garbat.<sup>14</sup>

Infection as a cause of disease of the gall-bladder and bile ducts has long been recognized. Early experience in surgical treatment showed a very high

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incidence of infection. More recent reports, however, have shown a distinctly lower percentage of positive cultures in the gall-bladder removed at operation. This is probably partly due to improved methods of diagnosis, which have led to the earlier recognition and surgical treatment of those patients having definite cholecystitis. Early treatment has probably many times prevented the element of infection from being superimposed upon other conditions, such as functional disturbances or cholelithiasis.

The actual incidence of biliary tract infection, as demonstrated from bacteriological cultures made at the time of operation, can be shown by a study of the literature. In regard to the bacteriological findings in bile removed from the gall-bladder at operation, Hartman<sup>15</sup> in 1903 reported an incidence of infection of 78 per cent, Rosenow<sup>16</sup> in 1916 55 per cent, Rovsing<sup>17</sup> in 1923 11 per cent, Judd, Mentzer, and Parkhill<sup>18</sup> in 1928 31 per cent, Branch<sup>20</sup> in 1929 reported 19 per cent. Hanssen and Yurevich<sup>21</sup> found in a series of 104 cases studied in 1935 that 20 per cent of operative bile specimens showed positive cultures. In the authors' present series of 120 patients the incidence of infection in the biliary tract as a whole was 24 per cent.

A complication in the pre-operative determination of biliary tract infection is the known fact that positive cultures may be obtained in a higher percentage of cases from the gall-bladder wall than from the gall-bladder bile. Thus Judd, Mentzer, and Parkhill<sup>18</sup> found positive bile cultures of the gall-bladder bile in 15 per cent of a series of 200 cases, whereas the gall-bladder wall proved positive in 40 per cent. Other investigators, however, have found lesser degrees of difference. Moynihan<sup>19</sup> reported 31 per cent positive cultures in the gall-bladder bile, 37 per cent in the gall-bladder wall. Branch<sup>20</sup> found the respective incidence of infection to be 19 per cent and 25 per cent, Hanssen and Yurevich<sup>21</sup> obtained 20 per cent positive cultures from the gall-bladder bile, 30 per cent in the gall-bladder wall.

In the past duodenal drainage has not proved entirely accurate as a means of demonstrating biliary tract infection. In 1921 Whipple<sup>13</sup> reported, in a series of 26 cases, a 50 per cent correlation between the cultures obtained at operation upon the biliary tract and those obtained in duodenal drainage cultures pre-operatively. In 1934, Lyon<sup>6</sup> reported that in 101 cases coming to operation the organisms found at operation had been found present in duodenal bile in the majority of cases; a detailed study of bacterial cultures was not reported.

The most detailed of the pre-operative and operative bacteriological studies which has come to our attention is that of Hanssen and Yurevich<sup>21</sup> of this clinic, who reported a series of 104 operative patients in 1935. In this group duodenal drainage cultures were sterile in 25 per cent of the cases, whereas at operation the biliary tract proved to be entirely sterile in 67 per cent of the patients. Therefore duodenal drainage indicated infection in 75 per cent of the patients, whereas operation proved infection in only 33 per cent. Furthermore 75 per cent of the positive duodenal cultures showed a

mixed growth of three or more types of organisms, while at operation only 5 per cent of the cases showed more than one. The predominating bacteria at operation were *B. coli*, streptococci, *B. typhosus*, and staphylococci. The duodenal cultures were predominantly staphylococci and streptococci.

The duodenal drainage reports of Hanssen and Yurevich<sup>21</sup> with 25 per cent sterile cultures, compare very favorably with other reports of similar work. The highest incidence of sterile cultures of duodenal bile in the literature is that of Buttiaux,<sup>22</sup> who in 1931 reported a series of 50 cases, with 42 per cent negative cultures. Garbat<sup>14</sup> in 132 cases found sterile cultures in 38 per cent, Whipple's<sup>13</sup> series has 15 per cent sterile cultures pre-operatively. In 1935 Lyon<sup>6</sup> reported a series of 905 drainages, having an incidence of 15 per cent sterile cultures. An extensive discussion has been published by Reh fuss and Nelson.<sup>23</sup>

These findings led Hanssen and Yurevich<sup>21</sup> to the conclusion that "the present technic for the bacteriological study of bile obtained by duodenal drainage is unsatisfactory because of the frequent occurrences in cultures of contaminating organisms from the pharynx, buccal cavity, and stomach." They further stated that "a technic must be developed which will eliminate or reduce to a minimum the confusion due to the presence of such contaminating organisms before cultures of bile obtained by duodenal drainage can be depended upon to supply reliable evidence of infection of the biliary tract."

Shortly after this publication Twiss and Phillips<sup>24</sup> reported an improved method of obtaining specimens of duodenal bile by means of an encapsulated duodenal tube.<sup>1</sup> The preparation of the tube and its use have been described in detail by Carter, Greene and Twiss.<sup>25</sup> In short, the bucket of a sterilized Twiss duodenal tube is covered with a keratin-coated gelatin capsule, which is dissolved off after the tube has entered the duodenum. Contaminations at the syringe end of the tube are eliminated as far as possible by the use of a 3-way stop-cock, through the side arm of which the bile for culture is collected.

The superiority of the encapsulated method in obtaining bile specimens for culture was demonstrated in the introductory article. A comparative study was then reported of 165 drainages upon a series of 50 patients, using both the encapsulated and "open" methods. The encapsulated method gave a considerably higher incidence of sterile cultures and more cultures of organisms significant of biliary tract infection than that found with the "open" method. Furthermore the encapsulated method gave a lower proportion of mixed cultures and types of organisms found in throats and gastric contents of the same patients.

Since this article was published there have been few reports in the literature about investigations of this character. Among these should be mentioned that of the German clinicians Kopnic and Melnik,<sup>26</sup> concerning the generally conceded diagnostic value of duodenal drainage in typhoid fever, and the favorable results of the Italian Repetto<sup>27</sup> in the diagnosis of active infections of the extra-hepatic biliary tract.

Pursuant upon the report of Twiss and Phillips<sup>24</sup> it is now our purpose to evaluate the results which have been obtained in a series of 120 consecutive operative cases which were studied in the Biliary Tract Clinic of the New York Post Graduate Hospital. In each case one or more pre-operative duodenal drainages were performed by the encapsulated method; the duodenal or dilute and the concentrated specimens of bile obtained were cultured under

TABLE I

Bacteriological findings in cultures of duodenal bile, 120 consecutive cases.

	Number of Cases	Per Cent
All cultures sterile.....	75	63
Positive cultures, 1 or 2 types of pathogenic organisms	32	26
Positive cultures, 1 or 2 types of non-pathogenic organisms.....	2	2
Positive cultures, 3 or more types of organisms.....	11	9
Total.....	120	

TABLE II

A comparative study of cultures of duodenal bile and specimens obtained from the biliary tract at operation.

<i>Bacteriological Findings</i>			
Number of Cases	Duodenal	Operative	%
<i>Sterile Cultures of Duodenal Bile</i>			
74	Negative	Negative	62
1	Negative	Positive	1
Total 75			
<i>Positive Cultures of Duodenal Bile</i>			
20	Positive	Positive identical	17
5	Positive	Positive similar	4
3	Positive	Positive different	2
17	Positive	Negative	14
Total 45			

the supervision of Dr. Adele Sheplar of the Department of Bacteriology. At the time of operation, specimens for culture were obtained of the gall-bladder bile, the gall-bladder wall, the cystic duct node, and stones if present. In patients having a choledochotomy, bile was taken from the common duct for culture. Evidence of infection was considered to be the presence of positive cultures of bacteria in any part of the biliary tract, or in any specimen of duodenal bile.

The results of the duodenal drainage cultures are shown in table 1. It is here seen that sterile cultures were obtained in all specimens of duodenal bile in 75 patients or 63 per cent of the series, and one or two types of organisms considered significant of biliary tract infection in 32 patients or 26 per cent. It is therefore apparent that findings considered satisfactory for diagnostic purposes were obtained in 89 per cent of the patients, whereas contaminations (non-pathogenic or mixed growths of bacteria) resulted in but 11 per cent.

A comparative study of bacteriological cultures of duodenal bile and of the specimens obtained at operation is shown in table 2. Here it is seen that 74 of the 75 patients having sterile cultures of duodenal drainage bile proved to have sterile cultures from all parts of the biliary tract at operation.

TABLE III

An analysis of the 28 patients having positive cultures in both the duodenal bile and operative specimens, showing the types of organisms found in the duodenal bile and in the biliary tract at operation.

<i>Bacteriological Findings</i>		
Number of Cases	Duodenal Drainage	Operative
8	Colon bacillus	Same
2	Colon bacillus-streptococcus	Same
8	Typhoid bacillus	Same
1	Non-hemolytic streptococcus	Same
1	Staphylococcus-streptococcus	Same
1	Colon bacillus-staphylococcus	Colon bacillus-streptococcus
1	Colon bacillus-streptococcus	Colon bacillus
1	Streptococcus-staphylococcus	Streptococcus
1	Colon bacillus-staphylococcus	Colon bacillus
1	<i>Bacillus proteus</i> -streptococcus	<i>Bacillus proteus</i> -streptococcus staphylococcus
1	Colon bacillus	Non-hemolytic streptococcus
1	Colon bacillus	<i>Bacillus proteus</i>
1	Streptococcus	Staphylococcus
Total 28		

Of the 28 patients having positive cultures both in the duodenal bile and in the biliary tract, 25 had the same type of organisms in the biliary tract that had been cultured in the duodenal bile. Of the remaining 20 patients having positive cultures of the duodenal bile, 17 were negative at operation and 3 showed organisms in the biliary tract different from those in the duodenal drainage bile.

An analysis of the 28 cases in which positive cultures were obtained in both the duodenal bile and the operative specimens is given in table 3. In 20 cases identical types of organisms were found in both the duodenal bile and the operative specimens, even when two types of organisms were found in the biliary tract at operation. In five patients two types of organisms were

found in the duodenal bile, whereas the operative specimens showed but one of these. In only three cases of this group, or 2 per cent of the entire series was there no agreement between the duodenal drainage and operative findings.

A summary of the 18 cases in which either positive or negative bacteriological findings in the duodenal bile were not confirmed at operation is given in table 4. In only one patient (number 46) a single sterile pre-operative specimen was not confirmed at operation. The biliary tract here showed a streptococcus. Seventeen other patients had positive cultures of duo-

TABLE IV

A summary of 18 cases in which the pre-operative and duodenal drainage cultures were at variance with the operative cultures. "M" specimens are obtained following stimulation with magnesium sulphate, "O" specimens after olive oil.  
("Mixed" cultures are those having three or more types of bacteria.)

<i>Bacteriological Findings</i>		
Case Number	Duodenal Drainage	Operative
29	Mixed—all three specimens	Negative
30	Mixed—all three specimens	Negative
31	Non-hemolytic streptococcus in the M-1 specimen only	Negative
	0-1 and 0-2 negative	
32	Mixed D-1 and M-1 specimens	Negative
	0-1 and 0-2 negative	
33	Mixed D-1 specimen only	Negative
	0-1 specimen negative	
34	<i>Micro. catarrhalis</i> -streptococcus in D-1 only	Negative
35	Friedlander bacillus	Negative
36	Colon bacillus	Negative
37	Mixed—in all specimens	Negative
38	Mixed—in all specimens	Negative
39	Mixed—in all specimens	Negative
40	Mixed—in all specimens	Negative
41	Mixed—in all specimens	Negative
42	Colon bacillus in all specimens	Negative
43	Mixed—one specimen only	Negative
44	Streptococcus in D-1 only	Negative
	0-1 and M-1 negative	
45	Mixed in all specimens	Negative
46	Negative—only D-1 cultured	Streptococcus

denal bile; in each the biliary tract was sterile at operation. The cultures labelled "mixed" were considered contaminations at the time of the drainage because of the presence of three or more types of bacteria, a finding never confirmed at operation. This conclusion seemed further justified because in most of these patients there were organisms in the duodenal bile such as the *Micrococcus catarrhalis*, pneumococcus, Friedlander bacillus, or the *Staphylococcus albus*, which are rarely if ever found in the biliary tract at operation.

Taking into consideration all cases in which the duodenal drainage bacteriological findings were not confirmed at operation, there was disagreement between the duodenal drainage and operative findings in 21 cases or 17 per



cent, of the total series. The diagnostic accuracy of the duodenal drainage findings may therefore be considered to be 83 per cent. By eliminating the 13 cases of disagreement obviously due to contaminations of duodenal bile, the diagnostic accuracy of those drainages considered satisfactory is increased to 93 per cent. It is hoped that more experience with the encapsulated method will further reduce the incidence of contamination of the duodenal bile.

### SUMMARY

1. In a series of 120 operative patients with chronic disease of the gall-bladder diagnostic duodenal drainages were performed pre-operatively, using the encapsulated Twiss duodenal tube.

2. Bacteriological cultures were made of the specimens of dilute and concentrated duodenal bile and of specimens obtained at operation from the gall-bladder bile, the gall-bladder wall, the cystic duct node, and stones if present.

3. Positive cultures were considered to be evidence of infection when found in any specimen of duodenal bile or in any part of the biliary tract.

4. A comparison of the pre-operative and operative bacteriological findings gave the following results:

(a) Sterile cultures of duodenal bile were obtained in 75 cases, in 74 the biliary tract proved sterile at operation.

(b) Positive cultures of duodenal bile without evidence of contamination were obtained in 28 cases, in 25 the same types of organisms were found at operation.

(c) Positive cultures of duodenal bile were obtained in 17 patients having a sterile biliary tract at operation, in 13 there was evidence of contamination of the duodenal bile.

5. The pre-operative diagnostic bacteriological findings were confirmed at operation in 83 per cent of the cases. Disregarding drainages considered unsatisfactory because of contaminations, the pre-operative and operative findings agreed in 93 per cent. Bacteriological cultures of duodenal bile obtained under sterile precautions, by means of the encapsulated duodenal tube, afford reliable evidence of biliary tract infection.

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# HORMONAL THERAPY FOR THE TREATMENT OF HIRSUTIES

## A Preliminary Report \*

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ALTHOUGH it is true that to date physiotherapy has been the chief means employed in the treatment of hirsuties and hypertrichosis in females, it is obvious that, whereas it has its merits, it is a form of therapy which does not in any way take cognizance of the etiological factors involved. Although it is true that the etiological factors in hirsutism and virilism have not been definitely established, there is sufficient evidence as found by many investigators to indicate that the root of this disturbance is a glandular dyscrasia which usually can be associated with a disturbance of the adrenals, the ovaries or the pituitary. The recession of masculine characteristics, even though temporary, which ensues after removal of an adenoma of the adrenal or of the ovary, or the recession or abatement of masculinizing characteristics which ensues after resection, in whole or in part, of a hyperplastic adrenal gland, suggested to investigators that it is a glandular derangement probably caused by the neoplasm or by the hyperplasia.<sup>1</sup>

I, too, believe that there is a glandular derangement involved in cases presenting hirsutism and masculinization even where no neoplasm is apparent. In a series of eight cases of hirsutism which I studied, I found that treatment with hormonal therapy in an attempt to regain glandular balance produced some surprising and promising results.

As a result, I am presenting for consideration the histories of this group of eight cases of females who presented such hirsuties and other masculinizing characteristics. My choice of cases for this series was in no way influenced by the results obtained with hormonal therapy; these cases were included merely because of the consecutive order in which they appeared for treatment when this study was undertaken.

The therapy administered by me in this series of aneoplastic glandular cases presenting hirsuties was based upon some of my own clinical observations, as well as upon the findings of Zondek, and Greenwood and Blythe; it was also in line with the observations and suggestions of Kurzrok. Zondek,<sup>2</sup> in his observations, found that estrone is rapidly absorbed when administered cutaneously. Greenwood and Blythe<sup>3</sup> found that the type of feathers in the capon could be modified by the cutaneous injection of estrone, so that at the local site of such injection the feathers changed to those of the hen, whereas the rest of the feathers on the body surface remained those of a capon. Kurzrok<sup>4</sup> and his associates found that the skin was very susceptible to the action of male hormone, so that in consequence it might re-

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spond by hirsutism even in the absence of any other masculinizing features. In hirsute females showing verified adrenal neoplasm and adrenal hyperplasia, Kurzrok<sup>4</sup> and other investigators<sup>5</sup> found that there is a preponderance of male hormone being produced in such cases, presumably by the hyperfunctioning adrenals, which checks the normal amount of female sex hormone that is being produced by the ovary. Kurzrok therefore suggested the possibility of suppressing the male hormone production by injections of estrone or its derivatives, not only by intracutaneous injection, but by inunction directly to the skin.

In view of the above, I attempted in my series the use of estrone by inunction and by hypodermic administration in some cases in an attempt to modify the hirsute areas directly and to flood the system with a product of the ovary in order to counteract the effects of the hyperfunctioning adrenal. In addition, in others, I attempted the use of a gonadotropic factor of the anterior pituitary gland, in an attempt to provoke stimulation of the ovary directly. By using the various types of therapy, I hoped to be able to study the responses to the varied therapy, both estrogenic and gonadotropic, and thus evaluate, if possible, the effects and benefits, if any, of these products in females presenting hirsuties and other masculine characteristics.\*

*Case 1*, aged 15 years, was referred for treatment because of hirsuties. She presented an overgrowth of moderately long, black, coarse hairs on the upper lip, chin, thighs and legs. Her menstruation had started one year ago, at the age of 14 years; it was regular for a while, but now occurs only every two to three months.

The patient was of the tomboy type. Her walk, dress, and mannerisms tended toward the masculine type. She did not like boys, but liked to partake of boys' games and was quite athletic.

The patient was obese, weighing 168 pounds; her height was 64 inches. The upper measurement (as measured from the top of the pubis to the heel) was 30 inches, the lower measurement (as measured from the top of the pubis to the vertex of the head) was 34 inches—a eunuchoid proportion. Her voice was gruff.

The mammae were prominent and contained glandular tissue. The labia minora were hypertrophied; the clitoris was enlarged to about 2½ cm. after retraction of the surrounding foreskin. The suprapubic hair was heterologous in distribution extending up to the umbilicus. Axillary hair was present. There was apparently no gross evidence of neoplasm in the pituitary, adrenals, or ovaries.

Roentgen examination revealed a closure of all epiphyses of the hand, wrist and elbow, and an apparently normal skull and sella turcica. The only significant chemical finding in the fasting blood was a cholesterol of 195 mg. and glucose of 86 mg. The Wassermann reaction was negative. The basal metabolic rate was plus 3 per cent at the outset of treatment. (At the end of treatment, it was minus 13.6 per cent and minus 9 per cent.)

An estrogenic hormone in small doses was given by hypodermic three times a week. After about two months of treatment there were slight but definite areas on the inner and anterior aspects of the thighs that were free from hair.

\* The amniotin for hypodermic use and in ointment form was supplied by E. R. Squibb & Sons, the theelin by Parke, Davis & Co., the progynon B by Schering Corporation—all estrogenic hormones. The emmenin—a placental extract of Collip having primarily estrogenic properties and some gonadotropic-like effect, for oral use, and an anterior pituitary gonadotropic factor (which contains also small amounts of other hypophyseal factors), were supplied by Ayerst, McKenna & Harrison.

An estrogenic ointment (this ointment contained 1000 I.U. per gram of substance) was then applied daily for about one month to the hairy region of the face, and to parts of the thigh, in addition to the hypodermics of estrone. The only appreciable effect resulting from the use of the ointment was a breaking off of some of the hairs at these local sites, but the roots remained. On the whole, the skin of the face became somewhat clearer, but there was no other effect except that the hair on the face seemed somewhat bleached. With this combination therapy the extension of the suprapubic hair to the umbilicus was still present, but the hair on the legs, though still present, showed areas of sparseness. After one month ointment was discontinued, but the hypodermics were continued for another two months.

At the termination of five months of treatment the patient had lost about 20 pounds on a restricted diet. Her menstrual periods were still irregular during the treatment. The clitoris was still prominent; the voice was not as gruff as originally; her gait and carriage seemed more feminine. The mother said that the patient was beginning to show an attraction for the opposite sex.

A report from her friends about one month after discontinuation of treatment indicated that she seeks the company of males, mixes well with females, uses rouge and face powder and even thinks of knitting. (These were foreign to her before.)

One and a half years later, at the age of about 17, the patient was rechecked by me. She informed me that she goes out with the opposite sex, mixes well with those of her own sex. Her periods have been regular since the discontinuation of her treatment; her flow is good, lasting three to four days. However, there had been regrowth of hair since treatment had been discontinued. The hirsuties of her legs, thighs and face was still present.

*Case 2*, 23 and married, appeared for treatment of obesity and superfluous hair growth. She had been treated at times for various glandular conditions. The patient was nervous, irritable, tired easily and was "lazy." Her menstrual periods started at 12 years and had been regular since. Her libido was not disturbed.

She weighed 162 pounds, was 51 inches in height, and presented normal body proportions. There was a marked hair growth on both cheeks, upper lip, chin and neck, which the patient had been accustomed to bleaching, in addition to frequent shaving of the neck and chin. The thighs and legs were completely covered with hair; the suprapubic hair extended up to the umbilicus. The clitoris was not enlarged.

There was no evidence on examination of any neoplastic pathology. The sella turcica was normal. The basal metabolic rate was 0 and plus 27 per cent on two different occasions. A fasting blood sugar was 90 mg.

The patient was placed on a restricted diet, estrogenic hormone by hypodermic several times a week, a placental preparation—emmenin—by mouth, and estrogenic ointment to be used by inunction on the face (100 grams containing 100,000 I.U. were used).

After two months of this therapy the patient showed complete loss of hair on the cheeks and neck. There was an occasional loose hair still present on the chin, but shaving was no longer necessary. There were moderately large hairless areas on the back of each thigh. As a whole the patient was much better in spirit, was more energetic, and had lost some of her excess weight. Her menstrual periods were not changed by the treatment. A follow-up was not possible.

*Case 3* (figures 1 and 2), aged 17, presented a marked hair growth on the cheeks and upper lip, and a moderate growth on her forearms, arms and legs. The patient dated the onset of the superfluous hair on her face from the age of 15, with more marked growth since that time. Her menstruation had started at 13 years of age, but was always irregular, skipping periods for several months. The periods were accompanied by headaches.

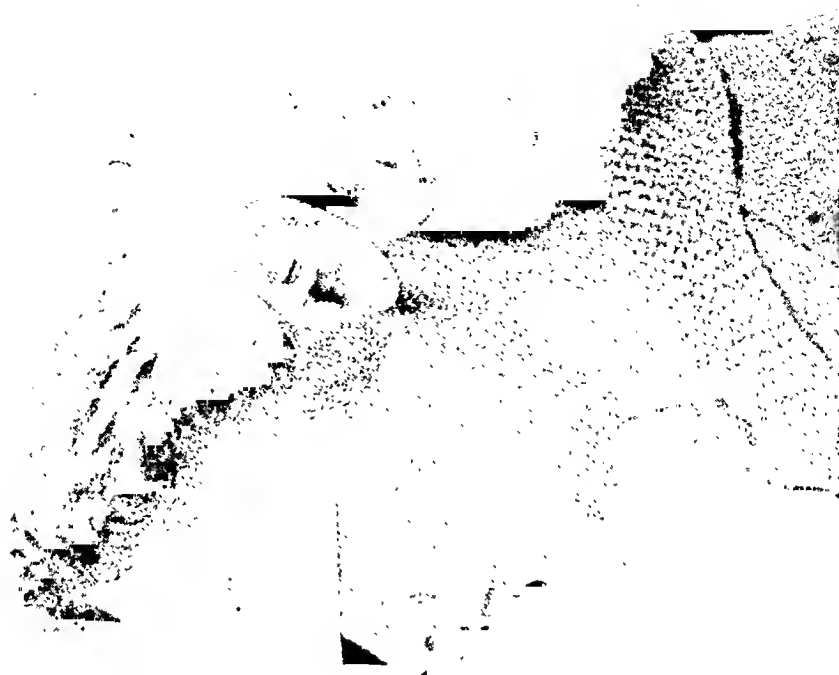


FIG. 2. *Case 3.* Five months after institution of hormonal therapy. Note complete loss of superfluous hair of face; note acne.



FIG. 1. *Case 3.* Before institution of therapy. Note hirsuties of cheek; much of the hirsuties is not apparent in the photograph.

Her weight was 113½ pounds, but she was prone to gain weight very easily if she did not watch her diet; her height was 60½ inches. The lower measurement was greater than the upper. Axillary hair was present. There was a moderate amount of hair on the inner and posterior aspects of the thighs and legs which the patient removed by depilatories. There was some hair in the sacral region. Pubic hair was present with a slight extension to the umbilicus. The clitoris was not enlarged. The breasts were well developed.

Roentgenograms revealed no existing pathology of the skull; all epiphyses of the wrist, hand and elbow were closed. The basal metabolic rate was 0.5 per cent. Her fasting blood sugar was 77 mg.

The patient was given an estrogenic ointment by inunction of the face. She used 200 grams of the ointment (200,000 I.U.) in a period of four months. Here, too, as in the previous case, there was a breaking off of some of the hairs and a bleaching of the originally dark hairs. One month after the use of the ointment there appeared to be an acne of the right cheek, and therefore ointment was applied to the left cheek only.

After three months of treatment with the ointment, an estrogenic hormone in moderate doses was given by hypodermic in addition to the estrogenic ointment. After one month of the latter combined treatment, without any marked perceptible effect, the hypodermics were discontinued. Subsequently, the patient noticed that the hair on the right cheek, where application of ointment had been discontinued, had now become sparser than that on the left cheek, where ointment was being applied—the reverse to that which existed before any treatment was instituted. Then the appearance of acne pustules on the left cheek necessitated a discontinuation of the ointment completely. The menstrual periods during the above treatment were still irregular.

An anterior pituitary gonadotropic factor by hypodermic several times a week was then instituted in addition to an oral placental hormone. Desiccated thyroid, gr. 1 daily, was added empirically. One day, after a month of this treatment, the patient informed me that the hairs on both cheeks were loose and that she had pulled them out completely and very easily. Examination showed that the hairs on both cheeks were almost completely out, with the exception of a few hair roots which were loosely embedded and could easily be pulled out. This was quite a change, since on examination only two days previously the hair growth was quite evident. However, about three weeks after the hairs had fallen out there began a regrowth of hair on the face. These hairs could be picked off very easily by pulling or by tweezer, something which could not be done prior to treatment because of the firmness with which the hair had been embedded. The patient also thought that some of the hairs on her legs had fallen out. It was noteworthy also that the abnormal hairs on the thighs, legs and abdomen could be pulled out very easily in contradistinction to the normal hair which still remained quite firmly embedded.

After about four months of the combined treatment including the pituitary gonadotropic factor, the placental factor was discontinued and the patient continued only with the gonadotropic factor for the next six months. During this time there had occurred a regrowth of hair on the cheeks, but this new hair was not quite as coarse as formerly; some hairs would fall out spontaneously at times, and almost all of the abnormal facial hair could be plucked out very easily by the patient at will. This was true, too, of the superfluous hair situated on the legs, thighs, abdomen, and in the areolar region.

During these nine months the patient had regular menstrual periods, with the exception of the last one which was three weeks overdue. Her breasts definitely had become fuller, her facial appearance more feminine. The patient discontinued treatment; a follow-up could not be made.

Case 4 was 23 and unmarried. Her complaint was that there was a thinning of the scalp hair and dandruff, an overgrowth of hair on the face and body, and a ten-

dency to gain weight very easily if diet was not watched. Her menstruation, which began at about 13 years of age, was always irregular and was preceded for two to three weeks by marked general discomfort and swelling of the breasts. Her libido was normal.

On examination there were noted some bleached hair on the cheeks, a slight amount of hair on the upper lip, many long coarse black hairs in the sternal region, many hairs on the back of the thighs, and some on the arms and legs. Pubic hair was present which extended along the midline to the umbilicus. Axillary hair was present. The breasts were pendulous and contained glandular tissue. The labia minora appeared somewhat hypertrophied; the clitoris was prominent (about 1 cm.). The patient stated that at times her voice would be a real bass, but at other times was not so low. It was, however, gruffer than it had been several years ago.

Her weight was 124 pounds; her height was 60½ inches. Her lower measurement was greater than the upper. The basal metabolic rate was minus 7.2 per cent. Total cholesterol in the fasting blood serum was 193, sugar was 73. Roentgenograms of the skull and osseous system were normal. The patient had a laparotomy two years ago for an appendectomy; both ovaries appeared macroscopically normal.

Local therapy was given for the seborrhea of the scalp. In addition, desiccated thyroid in small doses and a restricted diet were prescribed, and gonadotropic factor was given by hypodermic several times a week. After about two months of treatment the patient noticed that the hair on the legs fell out quite easily, that there was definitely a good-sized area on one leg free from hair, and that the remaining superfluous hair on this leg could be removed by the slightest pull, whereas that on the other leg was as yet firm. The suprapubic hair extending to the umbilicus also could be pulled out very easily, whereas the normal hair on the pubis was much firmer. The hair on the sternum was quite firm at this time.

After further injections, the hair on the sternum loosened and was easily extracted, as was the hair on the patient's cheeks below the normal hair-line. Other large areas free from hair were noted on the outer aspects of the legs. The seborrhea of the scalp had now cleared and the hairs on the head had become quite firm, although at the outset, due to the infection, these fell out very easily. During this period of treatment the patient menstruated regularly for two successive periods.

The above therapy was continued for many months. With it, the hair on the cheeks came out completely, that on the upper lip remained quite firm, and the abnormal hair in other regions fell out in spots or could be pulled out with ease.

However, after several weeks of this status of the hair, there was regrowth of the abnormal hair, but this new hair was finer and quite loosely embedded. The patient admitted that she was well pleased with the outcome of her treatment, since she had been dissatisfied with previous physiotherapy. On one occasion, when she had to wear a low-necked dress (a thing which she had shunned previously because of the hair growth on the midsternum), the sternal hairs had regrown to some extent, yet all she had to do was to apply gentle pulling and thus extract the chest hair. The patient was quite pleased with this accomplishment, and admitted that even though the hairs regrew it was quite an advantage to be able to extract them so easily. Of course attempting to pull these hairs prior to the initiation of the glandular treatment was quite painful and produced inflammatory reaction of the tissue at the hair roots.

For the past year, during treatment, her menstrual periods became more regular, varying in regularity by only a few days.

Five months after discontinuation of therapy the patient stated that although the facial and midsternal hair was regrowing she was quite pleased with the result, since these hairs were very slow in their regrowth, loose, easily extracted. The scalp hair in the fronto-parietal region was thinning out again and the dandruff was again present. Her menstrual periods were quite regular. She had married in the interim.



*Case 5*, aged 22, presented herself for treatment because of marked obesity, sluggishness, and an overgrowth of hair which had its onset four years previously. The patient's mother and sister also have abnormal hair growth, but not in any way like the patient's. Although the patient was a young girl, her appearance, due to obesity and facial hirsuties, was that of a matron. Her menstrual periods, which had started at the age of 13, were regular, the flow lasting about six days. She was unmarried.

The patient weighed 176 pounds and was 61 inches in height. Her lower measurement was slightly greater than the upper. Her breasts were pendulous, containing much fatty tissue and some glandular tissue. Nuchal and superclavicular fat padding was marked, as were the fat deposits elsewhere over the body.

Examination revealed no evidence of neoplasm. There was a marked hair growth on the chin, the neck, and on each of the outer portions of the upper lip. These hairs were long, black and coarse. Some excess hairs of a finer texture were noted on the cheeks. There was no hair in the sternal region and no marked overgrowth on the legs or thighs. Axillary hair was present. There was some slight extension of pubic hair to the umbilicus. All the abnormal hairs were quite firm when an attempt was made to pluck them. The clitoris was prominent (about 1 cm.).

Roentgenograms of the bony system revealed no apparent abnormality. The sella turcica was bridged. A fasting blood chemistry showed a total cholesterol of 212 mg., sugar 94 mg. Her basal metabolic rate was minus 7.2 per cent.

The patient was placed on a restricted diet and desiccated thyroid; gonadotropic factor was given by hypodermic several times a week.

After about three months of therapy, the patient noted that the hair on her chin, cheeks, and upper lip could be pulled out very easily, and, for the first time, she was free from hair. The regularity of this patient's periods, though, was somewhat disturbed; one period was skipped. On the whole, the patient felt much better. She had reduced 27 pounds in about four months, her appearance was much trimmer, and her social outlook was brighter.

Later, the superfluous hair regrew, as it had in the other patient, on the chin and outer margin of the upper lip, but these were not as coarse and could be pulled out very easily.

Of interest is the fact that prior to treatment, due to her appearance, she could not obtain employment. Since then she has passed a physical examination for a civil service position.

*Case 6*, aged 18 and unmarried, had not menstruated for the past year. Her periods had begun at the age of 13 years, but had been irregular ever since. At the beginning, her flow was fairly good; subsequently, it became very scanty. Occasionally her breasts would hurt a little before her periods. She experienced general weakness. The patient admitted the existence of a normal libido.

The patient appeared malnourished. Her weight was 107½ pounds, her height was 62 inches. The body proportions were eunuchoid (lower measurement was greater than the upper measurement). Her facial appearance and body contour were more of the masculine type. There was an occasional acne papule on the face and back.

There were a few blonde lanugo hairs on the chin and upper lip. Hair was present on the midsternum (noted by the patient for the past two years), and there were a few long hairs in the areolar region of the mammae. There was abundant hair present in the axillary regions and in the suprapubic region, but the latter extended to the umbilicus. There was also hair present on the posterior aspects of the thighs, legs, sacral region, and some on the forearms. The hair was quite firm and resisted plucking. (The patient admitted that her mother also had some excess hair on her thighs and legs, but none on the abdomen or face.)

The breasts were moderate in size, but the patient stated that they had not in-

creased in size lately. The external genitals appeared normal except for a somewhat prominent clitoris, which was about 1 cm. in size, suggesting a miniature phallus.

Roentgenograms of the skull revealed no abnormality; those of the bony skeleton showed epiphyseal closure of the hand, wrist and elbow. The basal metabolic rate was plus 9.8 per cent. The patient did not coöperate for blood studies.

Anterior pituitary gonadotropic factor was instituted by hypodermic several times a week.

After about a month of therapy the patient had her first menstrual period in a year and flowed for about two days. The abnormal hair at this time was still firm to plucking.

After about two and one-half months of treatment some of the hairs on the anterior chest wall and abdomen were loosening, but most of them were still quite firm.

One month after the above period the patient experienced some drawing down pains in both groins, but no vaginal bleeding occurred.

Two months later, the patient experienced pelvic cramps and stained for three days. During this time the patient took on about four pounds of weight and definitely presented a more feminine facial appearance.

Two months after this last staining the patient had a good vaginal menstrual flow lasting two and one-half days. At this time, after about five months of treatment, the suprapubic hair of the abdomen could be easily plucked although the normal pubic hair was firm. Of interest is the fact that the patient was free from acne for a comparatively longer period of time than before treatment had been instituted.

At the end of six months of this treatment the patient had gained about seven pounds, felt stronger, was quite cheerful and hopeful, and appeared much more feminine.

*Case 7* (figures 3 and 4), unmarried, 21½ years old, was a non-obese individual who complained of acne of the face and back, and hirsuties. Her menstruation had started at the age of 11½ years. Although this was irregular at the outset, the periods soon adjusted themselves and became quite regular. Her flow in the past was usually three to four days, but lately was somewhat scantier. Her acne and hirsuties both appeared at the age of 13 years. The patient did not consider herself frigid, but, due to her condition, desire for social intercourse was repressed. The patient says that her father and brother are both extremely hairy.

The patient's facial appearance and body contour tended toward the masculine type. Her entire body surface, including even the dorsal surfaces of her feet and toes, was practically covered with long black hairs about an inch in length. The hirsuties was much more than one sees on the average male, but equivalent to that seen on some hairy males. There was marked hirsuties of the cheeks, chin and upper lip. The pubic escutcheon was heterologous. All the hair was firm and difficult to pluck.

The external genitals appeared normal. The labia minora were prominent and somewhat hypertrophied; the clitoris was not penis-like, but was slightly prominent on retraction of the foreskin. Her voice was feminine.

There was no evidence of neoplasm on clinical study. The fasting blood showed a cholesterol of 220 mg., glucose 75 mg. The basal metabolic rate was plus 4.5 per cent. Her weight was 97½ pounds, height 58 inches.

The patient was given gonadotropic factor by hypodermic injections several times a week.

After two months of treatment the patient found that upon rubbing the legs some of the hair would fall out. The patient admits that this was much more than had ever happened prior to treatment. At this time the hairs on the cheeks and chin could be plucked by me much more easily than originally. The hair on the upper lip was still firm. The acne at times would clear up, only to reappear.

With continuation of the treatment there were noted small areas on the cheeks and the lower two-thirds of the legs that were free from hair.

The patient has now been under treatment for 10 months, but the best that could be done for her so far has been to bring about a more feminine appearance, a loosening

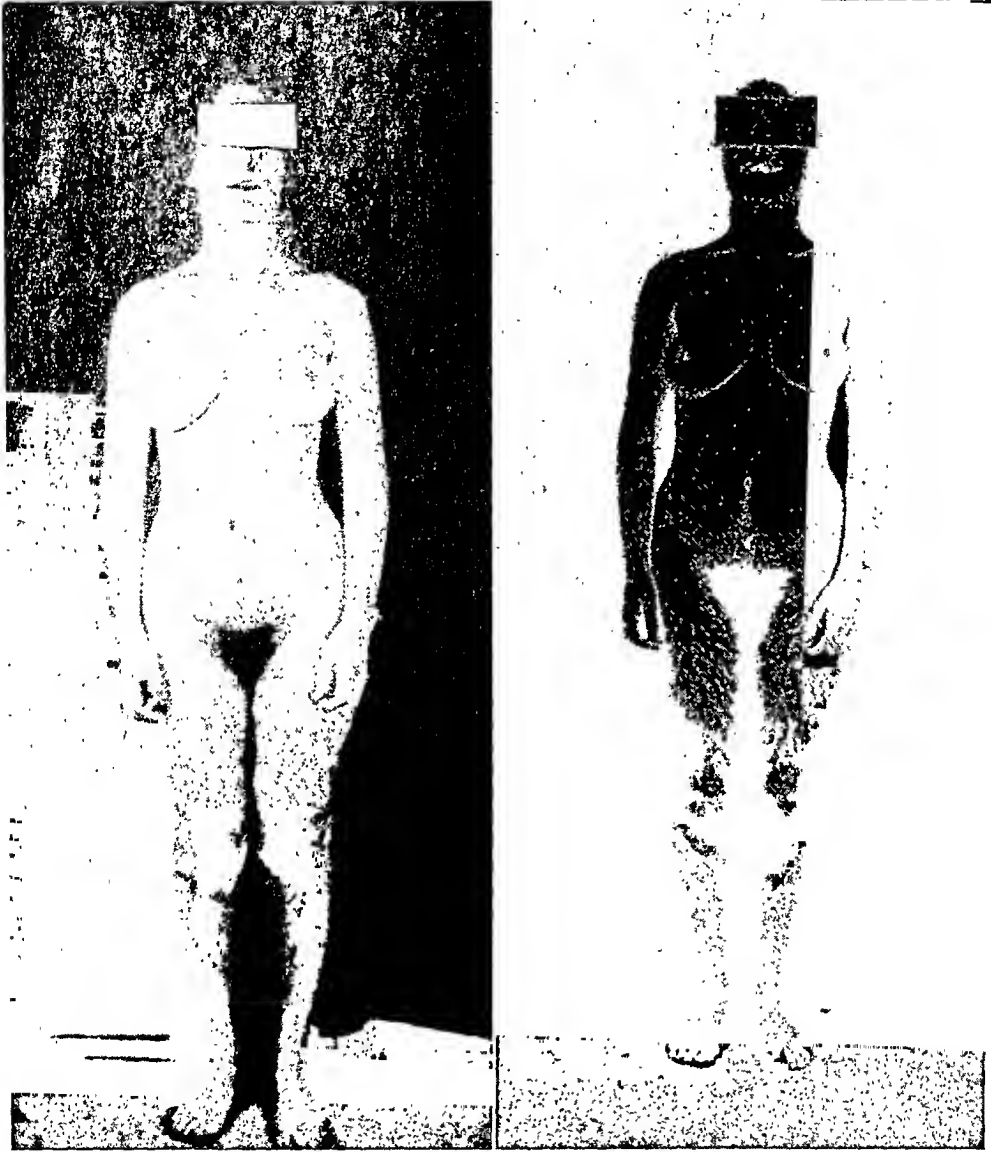


FIG. 3. (Left) *Case 7*. Note marked hirsuties before institution of hormonal therapy.  
FIG. 4. (Right) *Case 7*. Note legs after 9 months of hormonal therapy. The hair in parts was plucked quite easily by the patient.

of some of the hair on the cheeks and chin, which could be plucked with more ease than originally, and a loosening of the hair on the lower two-thirds of the legs which the patient was able to pluck almost completely and with ease. The rest of the body hair, including that on the upper lip, is still quite firm to plucking. It was attested by others in the office that the patient's appearance had become more feminine.

In view of the experiences in the other cases treated, I was disappointed in the

slowness of response to the therapy. However, this was one of the worst cases of hirsuties I had ever seen, and any favorable response such as was attained here, as evidenced by the loosening of the hair on the legs and in part on the cheeks and chin, was gratifying.

Later, in this case too, although therapy was still being administered, there was regrowth of hairs on the cheeks and chin, and, although these could be plucked, they resisted plucking much more than did the other cases treated similarly. Also, the periodicity of several of her menstrual periods had been disturbed. She had gained seven and one-half pounds.

At one interval, during the course of treatment, this patient also received, for about one month, large doses of estrogenic hormone, with no radical response.

*Case 8*, aged 15½, presented herself for treatment because of her obesity. At the age of nine or so, the patient was said to have a basal metabolic rate of minus 33 per cent and had taken oral thyroid medication. At the age of 13 years, the patient had enuresis and vaginitis, and was treated by "thyroid medication and by injections," with consequent correction of the two conditions. In view of her suspected glandular dyscrasia a repeat basal metabolism was given when she was 15 years old, and a rate of minus 15 per cent was found. The thyroid medication had been continued intermittently to date. Her menstrual periods had started at 12, were fairly regular, except during her injection treatment for vaginitis, and lasted for about three days. The patient was somewhat behind in her school work.

The patient weighed 174 pounds, and her height was 63¾ inches. The lower measurement was greater than the upper. Some pastiness and mild acne of the face were present. There was moderate hypertrichosis of both cheeks, as well as some light-colored hairs on the chin. The breasts were pendulous and contained glandular tissue. An occasional hair was present outside of the areolar region of the mammae. Axillary hair was present. There was a moderate amount of hair on the inner and posterior aspects of the thighs, and in the lumbosacral and gluteal regions. The pubic hair extended up to the umbilicus. There was a slight prominence of the clitoris.

Roentgenograms of wrist, hand, and elbow revealed closure of all epiphyses. The skull and sella turcica were within normal limits. The basal metabolic rate at the first examination was minus 3 per cent. (The patient had been taking three grains of thyroid medication per day.) The patient did not coöperate for blood studies.

A restricted diet was prescribed, desiccated thyroid was continued, and in addition gonadotropic factor by hypodermic injection was given several times a week. After a few weeks of treatment, the patient informed me that the hairs on her face came out very easily when she pulled at or touched them.

With the continuation of the treatment the patient was able to extract easily all the facial hair.

After three months of therapy the patient had lost about 15 pounds and was doing much better in her school work. Her menstrual regularity was not disturbed. The acne disappeared at times, only to reappear. The patient is still under treatment.

## DISCUSSION AND COMMENT

In the eight cases presented for consideration no definite neoplastic pathology in the adrenal, ovary or pituitary glands was found on clinical examination. All the patients showed some symptoms of masculinization, as evidenced primarily by hirsuties of the face, trunk and extremities, as by heterologous formation of suprapubic hair, some exaggeration of the size of the clitoris, and, in more than half of the patients, by irregular or scanty menstrual periods. In addition, upon examination, nearly all the cases re-

vealed a reversed body proportion, in that the lower measurement, as measured from the top of the pubic bone to the heel, was greater, to some extent, than the upper measurement, as measured from the pubis to the vertex of the head, a so-called eunuchoid proportion one usually associates with hypogonadism.

With the exception of case 8, where the basal metabolic rate was not indicative, due to the fact that desiccated thyroid had been taken for years because of a suspected thyroid insufficiency, all the cases showed basal metabolic rates which were not significant.

Obesity was a distinct factor in half of the cases; in two of the other cases there was a tendency toward obesity if dietary restrictions were not observed. It is believed by some that obesity is a factor in cases of adrenocortical hyperfunction, for they believe that the adrenal cortex is instrumental in the regulation of fat metabolism and that the cortical hormone has the ability to fix the fats in the tissues.<sup>6</sup> They also believe that weight reduction is difficult in such cases.<sup>7</sup> In my cases, I am not at all certain that such obesity was actually caused by the same glandular derangement as was causing the hirsutism. Furthermore, the customary low blood serum cholesterol value found by these investigators<sup>7</sup> in their cases was not found by me; rather the opposite was found to exist, namely, relatively high total cholesterol values in four cases—two of which were obese, one of which showed a tendency toward obesity, and one case which was non-obese. Also, weight loss could be and was accomplished in those of my series either by dietary restriction alone, or by diet and the addition of desiccated thyroid.

The values for blood sugar taken in six cases tended towards the lower normal values and probably indicated an increased sugar tolerance. In five of the cases where urine tests were done and recorded prior to the onset of hormonal treatment glycosuria was not evident. Hypertension was not a factor in any of these cases.

Prior to the initiation of therapy an attempt was made to judge the firmness with which the hairs were embedded. This was judged by the amount of pull needed in plucking with forceps. Although a somewhat crude method, it gave some idea of the firmness of the hairs. In all cases the existent hair, both in normal and abnormal sites, was embedded quite firmly, and attempts at plucking were difficult and painful to the patient; also, when these hairs were extracted, there usually was produced an inflammatory area at the site of extraction.

Although hormonal therapy did not produce complete eradication of the hirsuties in this series of cases, it nevertheless was noteworthy in that it provoked enough important changes to lead one to believe that it might be a stepping stone towards improved therapy; for it was found that after therapy had been administered for a time a spontaneous falling out of some of the superfluous hairs on the cheeks, chin, parts of the thighs and legs had taken place for the first time in most of the cases. In addition, in all of the

cases, at some time during hormonal treatment, the superfluous hair which had not fallen out spontaneously began showing a loosening at the roots. This occurred in the hirsute regions of the cheeks, chin, mid-sternum, abdomen, and parts of the thighs and legs. It was found then that when such loose hair was gently pulled, or when the hirsute area was gently rubbed, there was a falling out of the hair. This loosening or spontaneous falling out of hair did not, however, occur in all hirsute areas at the same time; nor did it follow a definite pattern. For example, in some, there first appeared small denuded areas on the parts of the thighs, with the superfluous hair on the rest of the thighs and the superfluous hair on the other parts of the body remaining firm and not responding until further therapy had been administered. In others, the hair on the cheeks loosened or fell out first, whereas the rest of the superfluous body hair remained firm until further therapy had been administered. On the whole it was found that the superfluous hair on the upper lip was most resistant to therapy, even though the superfluous hair on the cheeks and chin responded readily. In all cases, with but one exception (case 7), most of the hirsute areas showed some response, in varying degrees, so that even where some of the superfluous hair did not actually fall out, it at least loosened at the roots and thus lent itself to easy extraction. Even in the exception, the worst case of hirsuties the writer has ever seen (case 7), where the abnormal hair was more resistant to treatment than it was in the other cases, there was eventually a loosening of some of the abnormal hair on the cheeks, chin, and especially on the legs and forearms, which could be plucked more easily.

It is of interest that in several of the patients in this series, there was a familial tendency to superfluous hair formation. However, in spite of this apparent hereditary factor, there was the same response to hormonal treatment in these cases as there was in those presenting no hereditary tendency.

Such good effects on hirsuties as were obtained were no doubt very gratifying. I found later, though, that this promising state did not remain entirely unchanged, for soon a change took place and the excellent results were comparatively short-lived. Within a period ranging from several weeks to several months, there began a regrowth. With this regrowth, though, a gratifying thing occurred; the new hair no longer appeared in its original stubborn or coarse state, but rather it now showed up with a lighter color and finer texture, and in a more loosely rooted state so that it could be plucked with ease without causing pain or inflammation. (These changes in hirsute females were in line with the observations noted by A. D. K. Peters.<sup>8</sup>)

While all of these changes were taking place in the hirsute areas, it was significant that the normal hair did not fall out, nor did it ever loosen. In one case (case 4) where a sparseness of hair was evidenced in the fronto-parietal regions of the scalp, and with it a case of seborrhea (for which local medication was used), there even occurred a regrowth of firm hair in that

region during hormonal treatment. It is true, though, that after hormonal treatment had been discontinued for three months, there was a regression and some of this hair again fell out and the area again was somewhat sparse.

Of significance, too, were the other accompanying changes which took place during the course of hormonal treatment. It was noted that in addition to changes in the hirsutism the menstrual irregularity tended toward correction in some of the patients, and in one case (case 6) several periods occurred after an amenorrhea of one year. It is true too, however, that in a few, where the menstrual periodicity had been apparently normal, a temporary disturbance then occurred, possibly due to treatment. Later though, with a subsequent check-up after therapy had been discontinued, it was found to have once more reverted to the normal. In all cases, though, whether the menstrual periodicity had been regulated or disturbed during hormonal treatment, the above-mentioned effects of falling out and loosening of the superfluous hair took place.

In addition, the general psychic outlook of most of the patients in this series was greatly improved, and a certain feminizing effect was reflected in the facial appearance and demeanor of most of them (as indicated in the case reports) after treatments had been in progress for a time.

With regard to the therapy administered, judging from my series of cases, which I realize is small, I found the following:

Of the four cases in which estrone by inunction was given it was found that very few significant effects could be attained. Of course, it is possible that the dosage of 1,000 I.U. in each gram of ointment was inadequate. The effects which were noted, though, were that after inunction a slight bleaching of the hair seemed to occur, and, at times, although the roots remained, there was a breaking off from the surface of some of the coarse hairs at the sites of application.

In one case where a combined therapy of inunction and injection of estrone was given it was found that, in addition to bleaching effects, there was produced some loosening and falling out of hair on the thighs, rather than just a breaking off of hair from the surface.

In other cases, where in addition to the local and hypodermic estrogenic therapy, oral administration of emmenin was given in an attempt to provoke ovarian stimulation, some striking results were attained. Emmenin, which is a product of the chorionic villi of the placenta having some gonadotropic-like effects in addition to its estrogenic effects and requiring the presence of ovarian tissue for its action, was given in an attempt to provoke ovarian stimulation. In one case (case 2) after administrations of emmenin, this combination therapy produced quite striking results, so that where shaving of the hair of the face had been necessary, now the facial hair either fell out or was loosened so that it could be plucked easily, and shaving became unnecessary. (It is unknown what the state of this patient was after she had discontinued therapy, for a follow-up was impossible.) In another case (case 3) where inunction and hypodermics of estrone produced

no results at all, the addition of emmenin provoked a response, and facial hair then began to loosen and become more sparse.

As can be seen from the effects listed above, estrogenic products had different effects on different individuals in this series; in some, injection or inunction of estrone produced good results; in others, it produced no effects, and only after emmenin was added was there some response to treatment. It is difficult to decide, however, even though emmenin did provoke a good response, whether this product was the initiating factor setting up the response, or whether it merely contributed in furthering the response already initiated by estrogenic therapy. It can be seen that evaluation of each product is difficult, particularly because I had so few cases with which to work.

It is possible, however, that the gonadotropic-like properties of emmenin may have been responsible for some of the good responses. I believe this to be likely in view of the fact that when a gonadotropic factor of the anterior pituitary gland was used and administered alone, in some of the other cases, decided effects on the hirsuties were evident in a short time. This occurred in all of the five or six cases where hypodermic injections of gonadotropic factor were given. In all it was found that this gonadotropic product could be counted upon to produce results no different from the ones obtained with estrogenic hormone, but that it could be relied upon to produce these results more definitely, more quickly, more consistently and more effectively.

What the underlying physiologic basis for the effect of this anterior pituitary gonadotropic factor on the hirsuties was, is not clear, but one is tempted to speculate that its action may have been by direct effect on the ovary. At present it is hard to find the reason why estrone, which is a product of the ovary, should not produce the same striking results as the gonadotropic factor, which apparently stimulates the ovary directly and produces female sex hormone or estrone. One would expect the substitution of the finished product of the ovary, namely estrone, to accomplish the same end result as the female sex hormone which is produced by the ovary itself through gonadotropic stimulation. Of course there is the possibility that some other physiologic action may be taking place other than the supposed action through the ovary. Be that as it may, however, it is not within the scope of this paper, at the present time, to delve into a theoretical discussion; nor is it justifiable to attempt at this time to make dogmatic statements without more definite proof in a larger series of cases. Suffice it to say that some therapeutic approach to the problem of hirsuties has been attempted which it is hoped will aid in stimulating further study of this problem.

#### SUMMARY AND CONCLUSION

An attempt was made to offer a more basic form of therapy to hirsute females who, I presume, had a glandular derangement in the form of a hyperfunctioning of the adrenal cortex and a disturbance of the ovary, with-



out clinical evidences of any apparent neoplasm in these glands. This study was comprised of a group of eight females, from 15 to 23 years of age, who showed hirsutism in degrees, varying from slight facial hair and body hair growth to such marked hair growth that it required shaving, and who showed, in addition, some exaggeration of the clitoris and some menstrual irregularities.

These cases were submitted to various forms of estrogenic and gonadotropic therapy, administered orally, hypodermically, and by inunction. The following responses were noted:

Inunction on the face with estrogenic hormone, given in three cases, produced a very slight bleaching effect in the area where the ointment had been applied, and at times a breaking off from the surface of some of the coarse hairs, with the roots remaining. It is possible that the dosage used in these cases was insufficient. No such effects were noted in areas where the ointment was not used.

A combined therapy of inunction and injection of estrone, given in one case, produced not only the same bleaching effects, and a breaking off of hairs from the surface of the face where the ointment had been applied, but in addition there was produced an actual loosening and falling out of some hair on the thighs.

Oral administration of a placental extract, emmenin, containing not only estrogenic, but also gonadotropic-like properties, was given in two cases, in addition to local and hypodermic estrogenic therapy. With this addition of emmenin to the therapy, in one case, even where previous estrone therapy had produced no apparent result, there was now provoked a loosening and falling out of some of the facial hair. In another case, there was provoked a falling out and loosening of the hair so that it could be plucked easily, thus eliminating the necessity for shaving. It was quite likely that the apparent good effect of this product was due to the gonadotropic-like property it contained, especially in view of the subsequent success attained with an anterior pituitary gonadotropic hormone.

Hypodermic administrations of a gonadotropic anterior pituitary hormone alone provoked definite, quick responses in the majority of the cases. With this product the effects on the hirsuties were the same as when estrogenic hormone had been used; there was the same falling out and loosening of superfluous hair, but this product was more satisfactory and more dependable in that it was more consistently efficacious and could be counted upon to act more readily and more rapidly.

Other hair, in the normal sites, did not, throughout treatment with any of these products, loosen or fall out—it remained, as before, firmly embedded and showed no change in texture. In fact, in one case where there was a seborrhea of the scalp and the hair of the head was thin and had fallen out, a regrowth and firmness of the hair occurred during the period of hormonal and local treatment.

Loosening and falling out of superfluous hair were produced in a varying degree with hormonal treatment in all of these cases. Later though, a regrowth occurred. This regrowth, however, was of a lighter color and finer texture, and was more loosely embedded, so that it could be easily extracted.

At this time it is difficult to predict what the status of the hair will be in the future after there have been a series of depilations.

Even with incomplete results, the present modification in the hirsuties has caused a modification in the psychologic outlook of these patients as reflected in attitude, appearance and behavior.

Changes also took place in menstrual periodicity. Usually, where the menstrual rhythm was irregular, it tended to correct itself during hormonal treatment. In a few, though, where there had been a regular periodic menstrual rhythm prior to treatment, there occurred a disturbance of this rhythm during treatment. This, however, on subsequent check-up in two cases after treatment had been discontinued, was found to have corrected itself.

I am well aware of the smallness of the number of cases included in this series, of the incompleteness of this study, and of the short-comings of the therapy; I am also aware of the difficulty in evaluating the individual hormonal products used here. Nevertheless, I have presented this paper at this time as a preliminary report, in the hope that it might be a stepping-stone towards further clarification of such types of cases, and that it may aid in the arrival of a more exact basic therapy.

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## PSEUDO-MEGACOLON \*

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### I

MEGACOLON is recognized, either clinically by the severe constipation it causes; or roentgenologically, by the increase in size and capacity of the colon. It is noteworthy, however, that extreme enlargement, as revealed by opaque enema, may not be found again on subsequent examinations <sup>4, 13</sup>; such instances are due to acute intestinal atony, which occurs, for example, in renal colic, and may be produced experimentally in man by distention of the renal pelvis.<sup>13</sup> Clinically, this transient disturbance has been known for a long time.<sup>11</sup> It does not show itself by definite symptoms, since the colon regains normal tone in the course of a day or two; moreover, the intensity of the primary colicky pain outweighs any other associated discomfort.

From this acute reflex disorder the condition hereafter reported differs by reason of its chronicity and its entirely different roentgenologic features. It was observed in two groups of patients: in the first (seven persons), as a pronounced anomaly which had developed in early childhood; in the second (22 persons), as a less characteristic disturbance beginning in the third or fourth decade.

The patients of the more illustrative first group (four male, three female; five Europeans, two Arabs) stated that they had "always" been severely constipated; in four instances, the parents asserted that constipation had actually begun when the patients were less than two years old. Ever since, spontaneous evacuation would occur only once in six, eight, or even eleven days. Except for a sensation of moderate heaviness and of a "hazy head" towards the end of this period, there were no other definite clinical symptoms. Every imaginable mode of treatment had been attempted, including diets, drugs, massage, physiotherapy, and "cures" of all kinds. Purgatives, after being taken for many years, finally failed to act, whereupon soap enemata were resorted to. The patients, who were about 20 years of age when first seen by us, now sought advice because they felt that the trouble was increasing; but close questioning elicited the fact that spontaneous calls to stool were as frequent (or infrequent) as in previous years; only the response to cathartics and enemata had grown weaker. All the patients were rather slender, though not undernourished; they did not eat much for fear of distention. Otherwise they did not belong to any common constitutional or emotional type.

In patients of the second group, the complaints were less marked but essentially similar. Constipation had developed in the thirties. Eighteen

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of the 22 patients were women in whom sundry diseases coexisted, such as old fibrous lesions in the lungs, infections of the biliary tract, the bladder, or renal pelvis, and the like.

In the patients of the first group, physical examinations did not reveal anything of significance. The abdomen was normal on palpation; there was no pain; and there were no signs of infection, nervous disease, or endocrine disorder. But the roentgen findings were almost identical in these seven cases. Opaque enema showed a perfectly normal colon; the opaque medium was evacuated spontaneously. Barium given by the mouth passed through

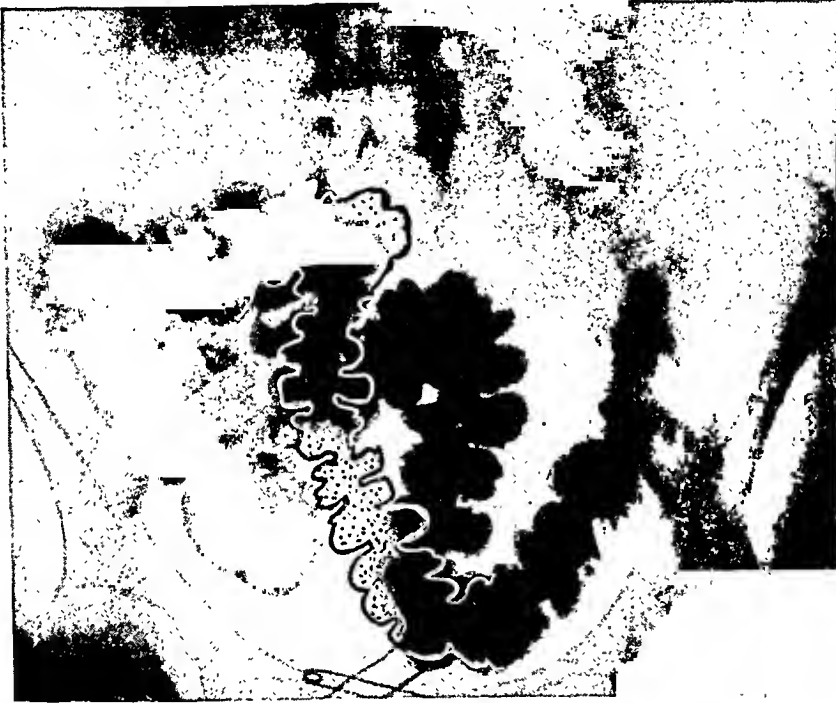


FIG. 1. Radiographs taken in the upright position at 6 feet (no distortion) under identical conditions, 5 and 5½ days after barium meal. The drawn contours indicate the position of the colon as traced from the second radiograph (5½ days). "Isomorphic" haustration. Opaque contents have not moved beyond splenic flexure. Serpentine mobility of transverse colon. A girl 21 yrs. old.

the stomach and small intestines normally; and 24 hours later, the ascending and transverse colons were filled. The haustration of the latter was particularly regular and uniform (isomorphic). There were no kinks or fixations. But, during the subsequent six or seven days, the opaque contents did not move beyond the splenic flexure. In two patients, serpentine movements of the entire transverse colon were definite during this period (figure 1), and haustral peristalsis was quite active. Within about 20 hours before spontaneous evacuation, particles of barium about one half the size of a haustrum were seen in the descending colon. Then, suddenly, the transverse colon was found free of barium, and the descending and sigmoid loops filled

with it. Defecation occurred a few hours later; the fecal material was rather dry, but not especially hard. Neither on palpation, proctoscopy, nor on roentgen examination, was any anomaly found in the rectum. The condition has nothing in common with dyschezia but the presence of constipation.

Very marked in the first group, these roentgen findings were less characteristic in the second; but it was common to both that the progress of barium was stopped, entirely or chiefly, at the splenic flexure; that the haus-

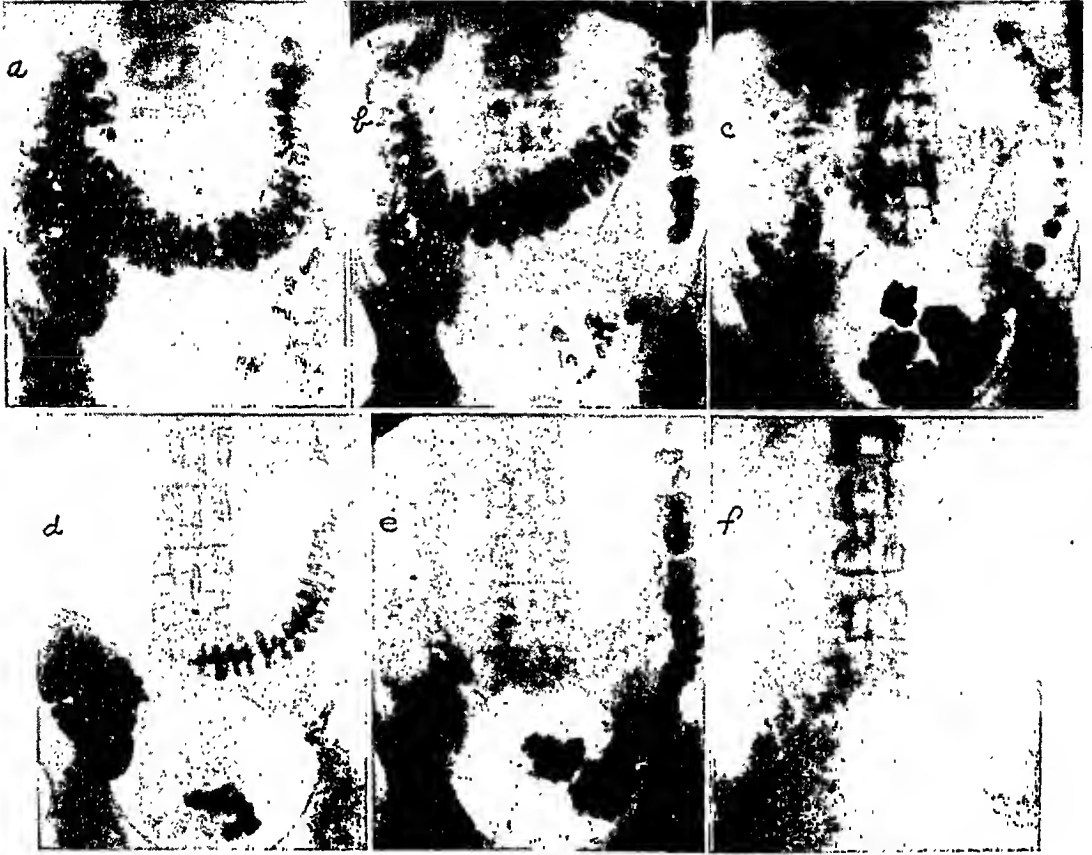


FIG. 2. Upper row: Colon 5 days (a), 9 days (b), and 9½ days (c) after barium meal. In (c) mass peristalsis has emptied the transverse colon. Lower row: Same patient three weeks after termination of pituitrin treatment. Colon 7 hours (d), 24 hours (e), and 48 hours (f) after barium meal. Mass peristalsis occurred between 7 and 24 hours after opaque meal. A merchant aged 24 yrs.

tration of the transverse colon was conspicuously regular; and that there was no retention in other parts of the colon, except for the slight physiological stasis which occurs normally in the cecum after the transverse colon has emptied itself.<sup>14</sup>

## II

In man, various influences modify colonic mechanics. Mental<sup>2, 16</sup> and climatic factors may be interlinked with the results of individual habits<sup>2</sup> and common customs.<sup>14</sup> Although a barium meal passes through the digestive

tract in a way quite different from the passage of normal food,<sup>1</sup> there is, at present, no better method of observation than roentgen examination, which shows that pendulum, rhythmic and stripping movements are often superimposed, corresponding to the simultaneous processes of absorption and transport. Individual and accidental variations may modify the appearances. In this variety, one mechanism stands out, namely, the caudad motion of the contents from the transverse into the descending colon by means of mass peristalsis. Preceded by a sudden disappearance of the haustra,<sup>2, 8</sup> mass peristalsis appears as a stripping tonic contraction<sup>5, 8, 14</sup> which, having its *point d'appui*<sup>2</sup> either above the cecum or at the hepatic flexure,<sup>2, 14</sup> constricts and stretches the transverse colon within about three seconds. The stripping or milking movement travels rapidly caudad, forcing the contents onward into the descending colon (figure 3), until activity ceases when the



FIG. 3. Normal mass peristalsis. Radiographs taken during the movement. By a stripping contraction, the contents of the transverse colon, spindle-shaped, are driven into the descending colon.

contraction reaches the splenic flexure. This "systolic" movement is normally preceded by a very much slower "diastolic" relaxation of the transverse colon<sup>14</sup> which, after having been completely filled from proximad, loses in tone and peristaltic activity very gradually in the course of from seven to 24 hours; this produces the downward curving and the isomorphic haustration characteristic of the position of rest.<sup>14</sup> If mass peristalsis sets in before this relaxation is complete, it empties parts only of the transverse colon; obviously, the "systolic" contraction is less effective when the "diastolic" slackening is either incomplete, defective, or impaired. This mechanism underlies various types of hypertonic and hyperkinetic constipation.

In the disorder here discussed, however, the transverse colon relaxed normally, and remained relaxed during an abnormally long period; mass movements, when they finally occurred, were normal in appearance and mechanical effect. Nothing, in fact, was wrong with the colon except for the ex-

treme prolongation of the interval between relaxation of its transverse portion and onset of mass peristalsis.

### III

Mass movements identical with the spontaneous ones can be induced experimentally in man by injection of 5–10 Voegtlin units of postpituitary extracts. Contraction occurs about 50 minutes after hypodermic injection, provided the transverse colon is relaxed.<sup>12</sup> In the patients here discussed, injection of pituitrin invariably induced mass peristalsis after this interval. Injection of simple saline solution (the nature of which was unknown to the patients), as well as of atropin and prostigmine, did not elicit any movements. Accordingly, the patients were given three injections weekly of 1 c.c. of pituitrin over periods of three to four weeks, with the result that constipation ceased immediately and normal bowel movements were maintained at least for several months after termination of the treatment. Recurrence was observed in three patients, but subsided after repetition of the series of injections. Four of the patients were observed during periods of from two to four years; in two of them, constipation did not recur at all after the first four injections; in one, there was one recurrence; and in the fourth, treatment has to be resumed about once a year. All sorts of lubricants and cathartics were entirely ineffective in these cases. No special diet was recommended. Enemas were forbidden, but two patients confessed that they resorted to them once in a while.

### IV

Constipation occurs in pituitary disorders,<sup>6, 7, 10</sup> where it may be associated with enlargement of the entire colon or parts of it<sup>10</sup>; it is also not uncommon when pituitary function is physiologically modified, e.g., in early pregnancy, before the uterus grows larger and presses upon the colon; and at the beginning of the climacteric. In these cases, as well as in acromegaly, we have occasionally found a general slowing down of colonic activity, but no isolated deficiency of mass peristalsis. The patients of our first group did not show clinical signs of pituitary disorder, although the disease had lasted some 20 years. Slight degrees of pituitary dysfunction, however, cannot always be ascertained by present methods, as normal variations merge with abnormalities of the endocrine formula. As to the therapeutic effect of postpituitary extracts, a clinician may be quoted who used to teach that, if a man was starved, and he put on weight when he was fed with steaks, this result did not prove beyond doubt that the starvation was necessarily due to a lack of steak-hormone in the blood. A correlation between normal or disordered mass peristalsis and the pituitary body is not established.

It is held that in Hirschsprung's disease the thickening of the colonic walls is the outcome of a primary disturbance of innervation.<sup>2, 9</sup> In spite of excessive stasis and definite reflex disorder of long duration, there was no colonic enlargement in our cases. The general roentgenologic aspect, the spontaneous occurrence of effective mass movements, and the results of pi-

tuin injections show that the intestinal walls had remained intact. The disturbance was not due to spasms, for it was not relieved by atropin and other spasmolytics; nor was it produced by purely mental factors, as injections other than of pituitrin failed to affect it. There was no abnormal position of the colon (which is very rarely responsible for constipation anyway). The absence of systemic symptoms in colonic stasis of such protracted duration does not support the old hypothesis of colonic autointoxication.

Exceedingly little is known about the correlations between normal and pathological motility on the one hand, and the processes of digestion, the vegetative system, the mind, and sundry extraneous factors on the other. Since these influences combine and overlap in the individual case, the notion that constipation is either essentially atonic or essentially spastic does not agree with this variability, nor with the wide individual and accidental variations observed roentgenologically. In this multiformity two well defined disturbances stand out: first, retention confined to the rectum, dyschezia; and, second, the disease above reported which is characterized by retardation of mass peristalsis, as is dyschezia by delayed contraction of the rectum. It is likely that from the study of such distinct disorders more information will be obtained about the normal motor physiology of the colon in man.

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# THE POPULARITY OF THE EWALD-BOAS TEST MEAL; REASONS FOR ITS SURVIVAL\*

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IN spite of all the criticisms directed against the orthodox method of gastric analysis involving the use of a carbohydrate test meal, it is still a favorite with the medical profession. Many clinicians are satisfied with only minor modifications. At the Mayo Clinic arrowroot biscuits and water are still used as the routine test meal. Objections directed against the single aspiration method and the Ewald-Boas test meal are, from a scientific point of view, well-founded, yet the advocates of this time-honored method of gastric analysis after administration of a meal of bread, crackers, biscuits or cereal, refuse to yield ground and maintain that for clinical purposes it is quite satisfactory, and in some respects superior to the newer ones. In 1925 Boas<sup>1</sup> reviewed arguments pro and con raised during the 40 years that the test meal, introduced by him in 1885, had been in use. He came to the conclusion that it still remained best for everyday use in clinic and in private practice. Since then there have been very few articles recommending it. In a presentation before the American Gastroenterological Association at its meeting in 1932, one of us<sup>2</sup> (Z. S. in collaboration with Drs. J. A. Marks and J. L. Kantor) stated that "our feeling is that for practical purposes it matters little what is used for a test meal or how many extractions are made. . . . It is only the exceptional case that will give low figures with one method and high ones with another." We are in full accord with the views promulgated by Eusterman<sup>3</sup> in his book, and readers are referred to it for a thorough and objective discussion of the question.

It is not the object of this communication to go into detailed discussion of the physiology of gastric secretion, the numerous types of test meal suggested, and methods of procedure advocated. An idea as to the variety of test meals used can be gained from the several references given below.

Boas<sup>1</sup> states that the earlier investigators (Leube, Riegel, Jaworski and Gluzinski) used egg albumin or beefsteak.

Isaak-Krieger<sup>4</sup> enumerates the following test meals, suggested by various authors:

Ehrenreich—milk, bread and other foods.

Skaller—soup, flavored with "maggi" (a concentrate used as a condiment).

Rehfuss—oatmeal gruel.

Schwartz and Seldine—bouillon.

Weitz—bouillon with sugar-color added.

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Galewski—tea.

Leschke—kimmel-flavored alcohol.

Ehrmann—dilute alcohol, 5 per cent.

Rothchild—"plasmon" solution (a protein drink).

Vandorfy—water.

Petrowych<sup>5</sup> quotes Talma as recommending the use of a solution of Liebig's meat extract. Also:

Kauber—3 per cent sugar solution.

Gorschkov—fish soup.

Leporski—white cabbage juice.

Katch—solution of caffenin.

Kaiser—a solution of "Maggi-wuerfel" (a bouillon cube).

Simnitski<sup>6</sup> suggested the use of a double test meal consisting of 200 c.c. of beef bouillon, giving one after fasting contents were aspirated, removing fractions every 15 minutes, emptying the stomach after one hour, then administering a second meal of 200 c.c. of beef bouillon and aspirating four more fractions at intervals of 15 minutes.

Fleckel<sup>7</sup> advises the same procedure, using Boas-Ewald test meals.

Makarewitsch<sup>8</sup> used bouillon of definite concentration, colored red.

Vandorfy<sup>9</sup> suggests that a Boas-Ewald test meal be given and aspirated in 45 minutes, and that seven days later two similar test meals be given at 45 minute intervals, and the stomach aspirated 45 minutes after the second meal.

Recently, acidity reduction tests were suggested as a part of the general study of gastric secretion.<sup>10</sup> This involves the introduction of decinormal HCl into the stomach and plotting a curve of reduction of acidity by fractional aspiration.

Many writers<sup>11</sup> consider the single aspiration as giving incomplete data, whereas others<sup>12</sup> consider the results obtained by the fractional method erroneous and misleading.

In evaluating the objections raised to the single aspiration method and to the use of a carbohydrate meal for the stimulation of gastric secretion, one must admit the crudity of the procedure, the frequent inaccuracies, and that at times the results obtained are unreliable. As stated above, it is for many reasons entirely unsatisfactory in accurate, scientific investigations. This was admitted by Boas and by other advocates of his method. For that matter, many of the modifications offered are also not free from objectionable features.

Recently Wilhelmij, reviewing the subject,<sup>13</sup> recommends the following changes in technic:

(1) The use of a more suitable test meal such as a specially prepared Liebig's extract solution. (2) Determination of the total secretions entering the stomach by adding phenol red to the test meal and determining the percentage of the original

meal left in each gastric sample. (3) Titration of the total acid in the sample, using an indicator which is free from the errors inherent in the use of phenolphthalein. (4) The separation of the total secretions entering the stomach into the fluid of the acid secretion and the fluid of the non-acid secretions. (5) Determination of the acidity of the total fluid secretions entering the stomach. (6) Discarding the determination of what are known as "free" and "combined" acid fractions.

We were considering the introduction of the above procedure in our clinic. It would involve the use of a solution of Liebig's extracts for the test meal, the employment of the fractional method in all cases, the use of brom-thymol instead of phenolphthalein as an indicator, and the addition of phenol red to the meal for the quantitative colorimetric estimation of gastric secretion and evacuation. However, before deciding on any change, we analysed our material for the past eight years. It was necessary that the advantages of the method proposed be sufficient to make up for the added discomfort to the patient and for the increased amount of work in the laboratory.

### MATERIAL AND METHODS

The material presented in this communication was obtained from one of the gastrointestinal clinics at the New York Post-Graduate Hospital.

We have been using in our clinic the following as a routine:

Five Uneeda biscuits and 400 c.c. of water were the test meal. Fasting contents were aspirated only when hypersecretion was suspected. Aspiration was done with a large tube (34 F. or 36 F.) 45-50 minutes after ingestion of the meal. If the contents were negative to Congo red, a Levin tube was passed and several fractions aspirated at 15 minute intervals.

A histamine test was done one or two weeks later when no free HCl was found by the fractional method, using Toepfer's indicator. In a number of cases, we also administered hypodermically 4 c.c. of a 1 per cent solution of neutral red, and observed the color of the fractions obtained. Those specimens which showed no coloration were acidified with HCl.

### RESULTS

In all, 2,153 gastric analyses by the single aspiration method were done. (Table 1.) There was ample free HCl in 1,909 instances, leaving 244

TABLE I  
Incidence of Achlorhydria in 2,153 Cases as Determined by Single  
Aspiration after a Carbohydrate Meal

Free HCl present in . . . . .	1,909 cases	88.7%
Free HCl absent in . . . . .	244 cases	11.3%
Total . . . . .	2,153 cases	100%

achlorhydrias (11.3 per cent). There were proportionately more cases of achlorhydria in women than in men. (Table 2.) About one-third of

TABLE II

Sex Distribution. Incidence of Achlorhydria as Determined by Single Aspiration after a Carbohydrate Meal

<i>Males</i> (1,087 cases)		
Free HCl present in . . . . .	974 cases	89.6%
Free HCl absent in . . . . .	113 cases	10.4%
Total . . . . .	1,087 cases	100%
<i>Females</i> (1,066 cases)		
Free HCl present in . . . . .	934 cases	87.6%
Free HCl absent in . . . . .	132 cases	12.4%
Total . . . . .	1,066 cases	100%

the achlorhydria cases subjected to the fractional method were found to be able to secrete HCl under the same stimulus (Uneda biscuits), leaving only 7.5 per cent in the achlorhydric group. (Table 3.) Sixty-four cases had

TABLE III

Free HCl Absent on Single Aspiration, Free HCl Present by Fractional Method

Total number of cases examined . . . . .	118	
Achlorhydria by both methods . . . . .	79 cases	67%
Achlorhydria in single aspiration; free HCl present by the fractional method in . . .	39 cases	33%
Total . . . . .	118 cases	100%

histamine by hypodermic injection. Of these, 15 had free HCl, which reduced this percentage to 5.6 per cent. (Table 4.) Twenty-six patients had

TABLE IV

Results of Histamine Stimulation in 64 Cases Found Achlorhydric by the Fractional Method

Free HCl present in . . . . .	15 cases	23.4%
Free HCl absent in . . . . .	49 cases	76.6%
Total . . . . .	64 cases	100%

4 c.c. of a 1 per cent solution of neutral red injected simultaneously with the histamine. All cases with free HCl also excreted the dye into the stomach. (Table 5.) It is interesting to note that in five cases there was neutral red

TABLE V

Neutral Red Excretion into the Stomach. Histamine Stimulation

Total cases receiving neutral red and histamine . . . . .	26
Free HCl and neutral red present . . . . .	10
Free HCl and neutral red absent . . . . .	11
Free HCl absent, neutral red present . . . . .	5

present in the gastric contents, where there was no free HCl after repeated stimulation with histamine. Thus, in about half the number of cases which showed achlorhydria by the single aspiration, no HCl was found by the other methods used.

In none of our cases was there any abnormality of the blood picture found during periods ranging from one to three years. Each of the achlorhydric cases had several complete blood examinations, including hemoglobin estimation, counts, and morphological study of the erythrocytes.

## DISCUSSION

Considering the fact that 89 per cent of all cases in which a gastric analysis was done showed free HCl in sufficient concentration by a single aspiration, using a carbohydrate meal, it seems to us that it is unnecessary to subject patients to the more complicated procedure of fractional aspirations. It would, from the clinical point of view, serve no useful purpose in nine cases out of ten. The tenth case may be reserved for more elaborate study. It is fairly generally conceded that the determination of the degree of gastric acidity is not of great diagnostic significance. Ehrmann<sup>15</sup> contends that exact determination of degrees of gastric acidity is unnecessary and unimportant. It suffices to judge, by the intensity of the bluish discoloration of the Congo red paper, whether the gastric contents contain a large, normal, low amount of free HCl, or none at all. Hyperchlorhydria or achlorhydria are not pathognomonic of any organic disease of the gastrointestinal tract. Indeed, either one is consistent with perfect health. Carlson<sup>14</sup> states that in normal persons gastric secretion may vary from hyperchlorhydria down to complete anacidity.

The different curves obtained by the fractional method, which were at one time considered peculiar for various pathological conditions, are no longer so regarded. Though some clinicians have entirely given up test meals as aids in diagnosis, they are, we believe, a small minority. Gastric analysis is so commonly used, because a great deal of information is gained by even the simplest test. At times gastric analysis clinches a doubtful diagnosis. Not infrequently the presence of ample free HCl makes the diagnosis of primary anemia quite questionable. Whereas carcinoma of the stomach may occur with a fair amount of free HCl, such an occurrence is nevertheless the exception. When the diagnosis is in doubt and the differentiation between chronic ulcer and malignancy comes into question, the finding of hyperchlorhydria will favor the former. Discovery of an unsuspected achlorhydria serves as an indication to modify the diet and the general management of a case. Hurst<sup>16</sup> considers achlorhydria as a precursor to gastric carcinoma. Bloomfield and his associates,<sup>17</sup> realizing the possibility of achlorhydria being a predisposing factor to the development of gastric carcinoma or pernicious anemia, started several years ago an anacidity clinic with the object of following these cases up for a number of years. Kahn<sup>18</sup> recently pointed out that, having examined 840 records of cases of pernicious anemia, there were no cases of peptic ulcer found. Most of the cases were proved to have achlorhydria, and Kahn assumes that all of them were achlorhydric. Thus, one can hardly expect a gastric or duodenal ulcer to develop in a patient showing achlorhydria. The lack of HCl in proved cases of gastric ulcer is recognized as a rarity and is probably due to a secondary gastritis.

## SUMMARY AND CONCLUSIONS

Gastric analysis is a worth-while procedure in all cases presenting any aberration of the digestive functions.

The single aspiration method and the carbohydrate test meal are satisfactory and give sufficient information in 90 per cent of cases.

The remaining 10 per cent may be further studied by the fractional method, using histamine, neutral red or any other method for the differentiation between true and false achlorhydria.

We believe that the procedure advocated by Wilhelmj is not applicable for routine gastrointestinal examinations in the clinic or in private practice. The greater accuracy and scientific value of the method proposed is, in the predominating majority of cases, far outweighed by discomfort to the patient and by the additional laboratory work, without adding anything of clinical value. Because of the considerable labor involved in this procedure, the tendency on the part of the clinician, if the precise method were advocated as a recognized routine for general adoption, would be to omit the test altogether. Thus, a valuable aid in the management of gastrointestinal disorders might be neglected and fall into disuse.

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# SOME OBSERVATIONS ON THE PERSISTENCE OF THE BACHMAN SKIN TEST AND OF EOSIN- OPHILIA AFTER RECOVERY FROM TRICHINOSIS \*

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THE value of the skin test in the diagnosis of trichinosis has now become definitely established through the researches of a number of investigators although the discovery of this procedure took place only 10 years ago. Bachman,<sup>1</sup> in 1928, showed that specific precipitin and skin tests could be obtained in experimental trichinella infections in laboratory animals. In 1932 his work was confirmed by Augustine and Theiler,<sup>2</sup> who first used the skin test as an aid to the diagnosis of trichinosis in human subjects. During the past eight years the skin test has been used in the investigation of a number of epidemics of the disease and in studies of sporadic cases as they have appeared in large hospitals. These reports<sup>3, 4, 7, 10, 11, 12</sup> indicate that the test is positive in from 70 per cent to 100 per cent of cases, and that it is of definite value as a diagnostic test.

Two distinct types of skin reaction to the Bachman antigen have been observed in trichinosis. The reaction peculiar to the earliest cases has been described by Spink<sup>3</sup> as delayed in type. He has recorded 5 cases in a series of 60, all but one with positive skin tests, who showed this delayed type of reaction. It was characterized by an initial flare which subsided quickly; then in 12 to 24 hours, at the site of injection of the antigen, there appeared a reddened, slightly edematous area from 1 to 3 cm. in diameter. This reaction, observed only in very early cases, reached a maximum within 18 to 24 hours and gradually subsided over a period of days. By the seventeenth day of the disease these five cases showed the more usual immediate type of reaction, characterized by a wheal and surrounding erythema which appears in about five minutes and is maximal within an hour. It is the persistence of ability to show this immediate type of skin reaction with which this paper is concerned.

There is but little available information regarding the length of time that eosinophilia and a positive skin test persist after recovery.

Augustine and Theiler<sup>2</sup> noted in their first publication that there was no marked difference in the intensity of the reaction elicited by the skin test in subjects early in the disease or in those obtained six months after the infection.

McCoy, Miller and Friedlander<sup>4</sup> tested 39 persons from three to twenty-

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two months after infection, of whom 49 per cent reacted to a 1:10,000 dilution of the antigen, and an additional 31 per cent reacted to a 1:500 dilution. Another group of 13 persons had been ill with trichinosis  $3\frac{1}{2}$  to  $7\frac{1}{2}$  years previous to the test. Of this group 23 per cent were positive to the 1:10,000 dilution and an additional 39 per cent reacted to the 1:500 dilution. Theiler, Augustine and Spink<sup>5</sup> reported the testing of five individuals who had been ill with known trichinosis from five to nine years previously. Two cases, nine and seven years later, showed negative skin reaction. The others, 7,  $5\frac{1}{2}$ , and 5 years later were positive. A 1:10,000 dilution of the antigen was used. Sobel<sup>6</sup> applied the test to five children with known past infections. One child reacted to the 1:10,000 dilution three years and eight months after the infection, another four months after the infection; a third child after  $3\frac{1}{2}$  years reacted to a 1:500 dilution but was negative to the 1:10,000. The other two, after  $3\frac{1}{2}$  years and 11 months, respectively, were negative to both the above dilutions.

From the Kiev Medical Institute in Russia comes a report by Kaljus<sup>7</sup> of a group of 66 cases of trichinosis. Forty-nine showed positive skin reactions and in three of these the first positive response was observed 120, 252, and 380 days, respectively, after the onset of illness. Of five other patients, four gave positive reactions five months, eight months, thirteen months, and two years after infection; another was negative after four years. The same antigen was used but in 1:1000 dilution.

A different approach to this matter was used by Schapiro, Crosby and Sickler.<sup>8</sup> They applied a 1:10,000 dilution of the Bachman antigen to 400 unselected patients in a municipal hospital. Simultaneously a study of diaphragms of those who came to necropsy was carried on. By the routine skin tests they found 18.25 per cent positive reactions; by a study of the diaphragms at post mortem 19.1 per cent contained encysted trichinellae. There were 73 cases with positive skin reactions; 27 of these subsequently came to necropsy and only three of the diaphragms were negative. Three hundred and ten cases had negative skin reactions. Eighty-nine came to necropsy and encysted trichinellae were found in the diaphragms of only two. In their study the immunologic and pathologic observations were made by different investigators.

Theiler, Augustine and Spink<sup>5</sup> found in the literature observations on persistent eosinophilia as follows:

3 months after infection . . . . .	8% eosinophiles (Staubli)
3 months after infection . . . . .	7% eosinophiles (Staubli)
6 months after infection . . . . .	34.7% eosinophiles (Brown)
6 months after infection . . . . .	7.1% eosinophiles (Staubli)
1 year after infection . . . . .	7% eosinophiles (Staubli)
3 years and seven months after infection . . . . .	8% (two cases) (Weindrack)

In a group studied by them two cases, 7 and  $5\frac{1}{2}$  years after infection, still had 5 per cent eosinophiles.

In another of Brown's<sup>9</sup> cases 16.8 per cent eosinophiles were found 16 to 17 weeks after the onset of symptoms.

The epidemic of trichinosis in Portland during February and March of 1935<sup>10</sup> provided an unusual opportunity to put the skin reaction to clinical test. Early in January of that year a prosperous Italian contractor purchased two pigs from a farmer in a nearby town. The pigs had been fed on garbage from an F.E.R.A. camp. In Portland they were fattened on corn and milk, slaughtered, and one of these pigs was sold on shares by the contractor to two of his employees. Most of the meat from this carcass was made into a favorite Italian sausage at home and dispensed widely among friends. The sausage was eaten raw or after very little cooking. All the cases of trichinosis in the epidemic occurred among those who had eaten the meat from this pig. Once the source of infection had been found, it was an easy matter to trace the dispersal of the meat, and in a sample of the pork obtained for microscopic examination encysted trichinellae were found. Seventy-one persons are known to have eaten of the infected meat, and positive skin reactions, eosinophilia, or both were observed in fifty-four. The study of the epidemic took place in February, March, and April, 1935. One or more eosinophile counts and skin tests were made on every person who had been exposed. A 1:10,000 dilution of the Bachman antigen was used for the intradermal test. Three years later, in March, April, and May of 1938, we undertook to retest these persons in the same way. We were able to retest 45 of the 52 survivors. The results are recorded in the appended table.

In the original study we reported the cases as follows:

Died .....	2
Persons ill with definite trichinosis but recovered: Every one of these individuals had eosinophilia and a positive skin reaction during his illness .....	22
Persons who had no symptoms but who had both eosinophilia and a positive skin reaction .....	9
Persons who had eosinophilia but negative skin reaction: This group includes two who were ill after having eaten the infected meat, but whose symptoms were not characteristic of trichinosis. Both these patients were treated at home by other physicians .....	16
Persons who were not ill, had no eosinophilia, but did have a positive skin reaction .....	5
Total .....	54

Of the 22 persons who were ill with definite trichinosis but recovered, 20 submitted to the tests three years later. Seventeen of them still showed positive reactions, and three were negative; thus 85 per cent had remained positive after three years. There was observed, however, a tendency for the reaction to be less striking. In five cases the reaction was approximately as marked as at the first test. One woman only had a more marked reaction when retested, 2 + instead of 1 +. The other 14 reactions at the more recent testing were less marked, 3, 2, or 1 + or 0 instead of 4 +. This change is in agreement with the observations of Theiler, Augustine and Spink on testing, after four to nine years, persons who had been hospital patients with the disease. Their two oldest cases, 9 and 7½ years after recovery, did not react to the skin test, while their three more recent cases did react.

Eight of the group of nine who had exhibited eosinophilia and positive skin reaction without symptoms were retested. Six of the eight still reacted; two did not. In four instances the reaction was of approximately the same degree. In four it was diminished or absent: thus 75 per cent of this group maintained their ability to react after three years.

Twelve of the 16 who had reacted to their exposure by showing eosinophilia alone were retested. Only one had developed a positive skin reaction. This unexpected reversal of the skin reaction was found in one of the two persons who had been ill after eating infected meat, but whose illness might not have been trichinosis.

The five persons found to have positive skin tests without eosinophilia at the time of the epidemic were retested. Four had lost their positive skin reaction. In one it had increased from 3 + to 4 +.

These last two groups are rather unsatisfactory for statistical analysis. Improperly cooked pork is considered a delicacy by these people of whom we speak, and the positive skin reaction without eosinophilia at the original testing may quite possibly have been the last sign of some previous infection.

TABLE I  
Comparative Skin Tests and Eosinophile Counts, 1935 and 1938

	Case	Age	1935			1938		
			Skin Test	Eosino- philes	Total W.B.C.	Skin Test	Eosino- philes	Total W.B.C.
Died	Mrs. A. F.	45		3 %	17,500			
	D. D.	40		24 %	12,000			
Persons ill with definite trichinosis, recovered	R. F.	44	4+	74 %*	15,000	4+	4 %	10,000
	D. F.	10	4+	19 %	12,800	2+	1 %	7,000
	A. F.	11	4+	51 %	9,400	3+	1.5 %	5,800
	T. F.	23	4+	12.5 %	12,000	1+	5 %	8,000
	J. F.	14	4+	50 %	15,400	3+	1 %	7,000
	R. F., Jr.	2	4+	70 %*	34,000	4+	4 %	8,000
	L. M.	32	4+	4 %	17,000	2+	2.5 %	6,900
	A. P.	22	4+	58 %	15,600	4+	1.3 %	9,500
	A. A.	55	4+	13 %	13,000	3+	.5 %	11,600
	C. F.	36	4+	33 %	12,200	3+	7 %	11,400
	P. F.	10	4+	38 %	23,000	3+	2 %	11,700
	Mrs. D. D.	44	4+	30 %	14,000	3+	3 %	6,800
	A. D.	17	4+	5 %	10,000	2+	1.5 %	14,200
	R. A.	45	4+	15 %	10,000	4+		11,000
	H. A.	23	4+	38 %	13,000	4+	1.3 %	5,000
	O. R.	21	4+	56 %	24,300	2+	1 %	13,800
	L. F.	7	4+	32 %	7,800	2+	7.3 %	10,000
	D. F.	13	4+	58 %	18,800	neg.	1.3 %	9,800
	Mrs. C. F.	35	4+	58 %	13,200	neg.	3.5 %	11,700
	O. B.	12	3+	33 %	19,600	neg.	5 %	6,000
	N. M.	14	4+	21 %	12,600			
	Mrs. R. A.	47	2+	8 %	11,000			

\* Highest of several determinations.

† Ill during the epidemic, symptoms not characteristic of trichinosis, treated at home by other physicians.

TABLE I—Continued

	Case	Age	1935			1938		
			Skin Test	Eosino- philes	Total W.B.C.	Skin Test	Eosino- philes	Total W.B.C.
Persons without symp- toms—eosinophilia and positive skin test present	Mrs. E. B.	48	2+	4.3%	12,500	1+	1 %	10,000
	L. B.	5	4+	39 %	15,100	3+	5 %	8,000
	T. A.	16	2+	6 %	17,600	2+	1 %	11,300
	F. A.	20	4+	6 %	9,800	4+		15,900
	M. A.	18	2+	9 %	13,200	2+	1 %	7,000
	A. D.	44	2+	7 %	13,300	neg.	4.5%	10,600
	T. D., Jr.	2	2+	5.5%	10,000			
	A. B.	11	4+	39.5%	15,700	neg.	2 %	7,100
	A. F.	8	2+	19 %	20,000	2+	3 %	8,900
Persons without symp- toms—eosinophilia pres- ent, skin test negative	J. M.	12	neg.	2.3%	22,900	neg.	4 %	13,600
	L. M.	10	neg.	10 %	17,000	neg.	6 %	11,800
	J. M.	8	neg.	7 %	20,000	neg.		
	C. M.	6	neg.	5 %	24,200	neg.	10 %	17,500
	A. M.	38	neg.	7 %	13,100	neg.	1.5%	
	E. B.†	33	neg.	28 %	14,000	3+	3 %	9,900
	J. B.	35	neg.	12 %	14,000			
	C. B.	10	neg.	21 %	13,000	neg.	1.5%	9,000
	M. B.	8	neg.	33 %	16,400	neg.	4 %	10,500
	J. R.†	7	neg.	23 %	14,000	neg.	3 %	12,200
	E. B.	48	neg.	4.3%	12,500	neg.	3 %	12,000
	N. D.	10	neg.	11 %	19,000	neg.	3.5%*	32,000
	A. D.	36	neg.	5 %	13,000	neg.	3 %	10,400
	S. D.	7	neg.	5 %	16,000			
	A. F.	12	neg.	7.5%	11,000			
	J. D.	4	neg.	10 %	13,000			
Persons without symp- toms—eosinophilia ab- sent, skin test positive	F. B.	13	3+	2 %	9,200	neg.	.5%	7,500
	F. O.	55	4+	3 %	8,000	4+	2 %	6,000
	M. N.	33	3+	2 %	6,000	neg.	2 %	7,800
	A. D.	33	4+	3 %	8,000	neg.	3.5%	9,400
	A. B.	21	3+	3 %	6,000	neg.	2.5%	7,000

Persistent eosinophilia of over 500 per cu. mm. was observed in six individuals in this present study. The total white counts and eosinophile percentages were as follows:

C. F.	7% of 11,411 = 798
L. F.	7.3% of 10,000 = 730
J. M.	4% of 13,600 = 544
L. M.	6% of 11,800 = 708
C. M.	10% of 17,500 = 1750
N. DiB.	3.5% of 32,000 = 1120
whose count one day later was	
	3.5% of 18,800 = 658

All these white counts are high normal or above normal so we do not care to draw any conclusions from them. They suggest that while eosinophilia is rarely present three years after infection with trichinellae, the leukocytic response to other ills may contain more than the usual number

of eosinophiles. It has, however, been shown that intercurrent infection in acute trichinosis causes the disappearance of eosinophiles in the blood smear.<sup>11</sup>

### SUMMARY

1. In persons who have been ill with clinical trichinosis the Bachman intradermal skin reaction remains positive after three years in the great majority of cases, although there is a tendency toward a less marked reaction.

2. In subclinical trichinosis with a negative skin reaction the skin test is also negative after three years.

3. Eosinophilia is usually absent three years after recovery from trichinosis.

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# THE USE OF HISTAMINE IN RHEUMATOID ARTHRITIS\*

By R. O. MUETHER, M.D., *St. Louis, Missouri*

THERE can be little doubt that arthritis and allied conditions are assuming a deservedly more important place in the thoughts of both the clinician and the research worker. In spite of much recent work, however, a satisfactory basis for treatment has not been established, and some treatments are expensive and complicated. Fever therapy, hydrotherapy, etc., seem to give great relief but are difficult of attainment under ordinary circumstances. The production of artificial jaundice advocated by Hench is difficult to obtain because of its dangers and expense.<sup>1, 2, 3, 4</sup>

It is true that certain forms of physical therapy can be administered in the home using improvised equipment, and all such measures should be employed since the more comprehensive and inclusive the treatment the more satisfactory will be the results.

Certain drugs having a vasomotor effect have been administered with some success by means of iontophoresis. This procedure requires a suitable apparatus for administration and to this extent is handicapped. Some drugs which are administered by iontophoresis will produce their effects when given by mouth or subcutaneously but the effects produced by such administration are not always as satisfactory as when the drugs are given by iontophoresis. Histamine diphosphate seems to be an exception. Histamine has been administered to arthritics in a variety of ways, with varying results. Medical iontophoresis is the method advocated for administration by most investigators. It has been given, however, by mouth, by injection, and as an ointment.

Our experience with the drug includes administration by ointment, subcutaneous injection, and iontophoresis. We have administered the drug by iontophoresis and succeeded in getting general reactions such as fall in blood pressure, flushing, palpitation. This method was time-consuming and difficult to continue after the patient left the hospital. We have used histamine ointment alone, mixed with a rubefacient such as capsicum, and also combined with various forms of salicylates. None of these ointments produced either general or local response of sufficient degree to be helpful, and our recent experiences with commercial preparations of histamine ointment have been no better. We then resorted to subcutaneous injections of histamine with the results reported in this communication.

Deutsch<sup>5</sup> was perhaps the first to report on use of histamine by iontophoresis. He had used other methods of administration but finally concluded the iontophoresis was the most satisfactory. Deutsch first used his-

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From the Arthritis Division, St. Louis University Group of Hospitals.

tamine in an attempt to simulate fever therapy, since he felt that the reactions associated with fever therapy arose from histamine-like reactions in the tissues. He pointed out that histamine was particularly efficacious in soft tissue involvements such as bursitis and fibrositis, and in this opinion we must concur. The polyarthritic according to Deutsch was benefited but never cured by the administration of histamine, and this has been our experience.

Kling<sup>6, 7</sup> in this country reported, rather enthusiastically, on the use of histamine in the treatment of arthritis. He experimented with various methods of administration and, at one time, scarified lightly the tissue about the involved joints and applied the histamine. In this way reactions could be obtained, but they were erratic and the scarifications took considerable time to heal, so that eventually the method was abandoned for iontophoresis. Kling and Sashin<sup>8</sup> brought out the fact that a combination of drugs given by iontophoresis may react better than one drug alone. Salicylates and histamine both given by iontophoresis seem to be such a combination. They also emphasized the advantages of histamine over other forms of physical therapy in soft tissue disease, finding that bursitis, tenosynovitis, and fibrositis responded well.

Shanson, Barnett and Eastwood,<sup>9</sup> working in England, reported favorably on the injection of histamine subcutaneously in arthritis. They used histamine diphosphate and thio-histamine and concluded that the diphosphate was the drug of choice.

#### PROCEDURE

In an attempt to evaluate the importance, if any, of subcutaneously administered histamine to the patient suffering from rheumatoid arthritis, the following study was carried out.

Ten patients suffering from rheumatoid arthritis were selected; the criteria being that only patients who had been followed by us for one year or more and who seemed likely to cooperate were to be used. No change in their therapy was made. Physical therapy, salicylates, exercise and occupational therapy were continued. In addition to these things, however, histamine injections were started. The frequency of injections varied with conditions but were essentially the same for a particular patient. Hospitalized patients were injected twice a day, ambulatory patients returning to the Outpatient Clinic were injected three times a week and other patients, who consented, were injected at home once daily by someone of the family trained in the use of the syringe. The diphosphate was the salt used and was supplied through the courtesy of Eli Lilly and Company. It was made up in Coca solution, in dilution of 1-1000. It was kept in dark bottles in refrigerator until used. The solution seems fairly stable and can be kept in a cool place outside the refrigerator, if necessary.

It was soon noted that the individual tolerancy to histamine varied and a test dose of 0.1 c.c. was given to each patient, this dose being increased by 0.1 c.c. until the reaction level was reached. This reaction-producing

dose was then maintained until the patient's tolerance increased. Increased tolerance was determined by failure to react to the usual dose. In our experience 0.4 to 0.6 c.c. is the range of effective dosage, and it is our experience that tolerance is only rarely increased, since patients who react to a given amount will continue to react at that level for three to six months.

The patients were told to report any change in symptoms and were also asked about their sensations immediately after injections. We attempted, so far as possible, to avoid suggesting symptoms which might be expected from the drug and we did not tell the patients in what way we thought they might benefit. Patients were urged to continue injections for one month and were then told that they might continue or not. It was felt that the patient would in that way evaluate the results of the treatment more accurately.

Only individuals suffering from rheumatoid arthritis are considered in this study.

### RESULTS

The immediate reaction to injection of histamine varies, naturally, with the size of the dose and the susceptibility of the patient. Patients vary considerably in their response to the drug, but each individual responds in essentially the same manner to subsequent injections. In none of the cases were the reactions severe enough to incapacitate the patient.

The chief symptoms noted are headaches, flushing, palpitation, sweating, nausea, dizziness and weakness. The headaches are rather constant, come quickly after injections, and are dull and throbbing; they are felt chiefly on the top of the head. The headache leaves in about 10 to 15 minutes unless too large a dose of the drug has been given. Flushing is also a common symptom. The patient notices a feeling of warmth, and the skin becomes red and warm to the touch. This lasts for 5 to 10 minutes and may be followed by a moderately profuse sweat. The flushing seems essential to the success of the treatment, since those patients who did not flush failed to get relief from pain and stiffness.

Palpitation was not a constant finding and was never alarming. Tachycardia was noted in all cases at the height of the reaction and it was at this point that nausea and faintness were occasionally complained of. It was at this point, too, that the blood pressure found its lowest level. The entire reaction rarely lasted 15 minutes and was never alarming. Following the reaction, relief from pain and stiffness was noted by most patients. There seem to be few contraindications to the use of histamine in the amounts used by us. Senility, marked vasomotor instability, marked arteriosclerosis, cardiac decompensation and hypotension would seem to represent conditions in which the drug should be administered with great caution or not at all. Table 1 gives a brief resumé of duration, sex, principal joint involvement, etc. in this group of cases.



TABLE I

Number	Sex	Age	Type	Duration	Primary Symptoms
6986	M	30	Rheumatoid arthritis	7 yrs.	Deformity, fixation and stiffness.
2040	F	54	Rheumatoid arthritis	3 yrs.	Swelling of joint. Weakness. Mild deformity.
4270	M	22	Rheumatoid arthritis	4 yrs.	Marked deformity. Limitation of motion and stiffness.
1042	F	29	Rheumatoid arthritis	2 yrs.	Slight deformity. No fixation. Pain.
5706	F	42	Rheumatoid arthritis	5 yrs.	Marked deformity. Fixation and stiffness.
1070	M	27	Rheumatoid arthritis	4 yrs.	Fixation of back, hips and knees. Marked stiffness.
H22518	F	43	Rheumatoid arthritis	11 yrs.	Deformity and fixation of joints of lower extremities.
39682	F		Rheumatoid arthritis		Deformity and fixation of lower extremities. Upper less markedly involved.
36-9198	M	35	Rheumatoid arthritis	6 yrs.	Fixation of neck, hips and knees.
34-9228	F	42	Rheumatoid arthritis	4 yrs.	Fixation of knees and involvement of upper extremities.

Table 2 is an attempt to present the results in a compact form. It will be noted that of 10 cases, seven were definitely benefited, inasmuch as increased motion and, in most instances, relief from pain were noticed. All of these patients felt that their extremities were warmer than usual and there was a sense of well-being which they had not noticed for some time. This sense of improved well-being manifested itself in numerous ways. Increased activity, improved appetite, greater cheerfulness were some of the subjective changes noted. Physical therapy was less tedious since it was less difficult for the patient to be moved about.

One of the seven patients, who admitted relief from stiffness, objected to the injections to such an extent that they were discontinued after two and one-half months.

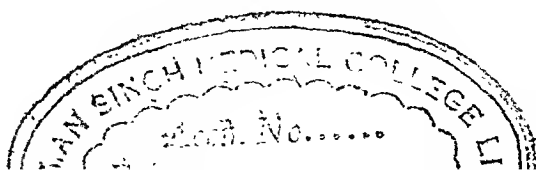
There are three failures, and a brief analysis of these is of interest. Case 6986 was a young man 30 years of age who had had arthritis for seven years. He had a complete ankylosis of the spine and the hips were fixed. He had had manipulation under anesthesia at another institution, and roentgen-ray examination of hips when he entered the Firmin Desloge Hospital revealed bilateral fracture of the necks of the femurs. The head of the right femur was practically absorbed. He had a positive gonococcal fixation test, pus in the prostate, and fissure in ano. It is felt that, in spite of the

TABLE II

Number	No. In- jected	Dose	Duration	Reaction	Results
6986	65	2-6 minims	2 mos.	Flushing Sweating Nausea (mild)	Noted slight improvement in motion but this did not persist.
2040	36	4-8 minims	3 mos.	Dizziness Headache Sweating	Marked increase in motion. Diminished pain. Improvement has persisted without treatment for 3 months.
4270	32	6 minims	3 mos.	Headache Flushing Sweating	Marked improvement in motion which has persisted for 9 months.
1042	19	6 minims	19 days	Flushing Palpitation Sweating	No beneficial results and refused more injections.
3706	130	10 minims	3 mos.	Flushing Headache Palpitation Sweating	Noted increased motion during injections and requested continuation — no permanent results.
1070	280	10 minims	5 mos.	Flushing Nausea (mild) Headache Sweating	Felt much better during treatment. Stiffness improved to point where patient was up and about. Improvement persisting.
H22518	725	10 minims	2 yrs.	Flushing Headache Palpitation	Was able to move about after injections — effect noted for from 4 to 6 hours.
39682	60	6 minims	2 mos.	Headache Palpitation	Patient felt only slightly helped and injections were discontinued.
369198	105	6-8 minims	3 mos.	Nausea Palpitation Sweating	Noted increased motion after injections and diminution in pain.
34-9228	85	8 minims	2½ mos.	Palpitation Flushing Abdominal discomfort	Patient objected to the injection and although motion was improved treatment was discontinued.

distribution of the arthritis and the roentgenograms which were more or less characteristic of rheumatoid arthritis, this patient was suffering from polyarthritis of gonorrheal origin. This form of arthritis is not rare and taxes the ingenuity of the best diagnostician. In fact, it is impossible in the late stages to differentiate it satisfactorily from rheumatoid arthritis. In any event the patient showed only a slight and temporary improvement on histamine to which he was, incidentally, quite sensitive and, after two months, injections were discontinued.

The second failure, case 1042, was a female, 29 years of age, with early rheumatoid arthritis. She had 19 injections of the drug, got satisfactory



reactions, but did not feel that they helped her and, after 19 days, refused more injections.

The third case, 39682, was also a female with quite marked involvement of the legs. The knees were fixed in flexion, and there was limitation of motion of the hips. This patient took daily injections for two months, had definite increase of motion in the hip joints, and was able to walk with the aid of a cane. The staff considered her a case which had been aided by injections, but she felt that she was very little benefited. She asked that injections be discontinued; this was done and she was classed as a failure.

Of the other cases treated, most drifted away from the treatment after periods of from three to five months. One case stands out because of the duration of the treatment.

Case 22518, a very intelligent, coöperative school teacher, when first seen in the clinic was unable to work and without funds. She improved on physical therapy, massage, etc., but continued to be extremely stiff on awakening in the mornings. Her "limbering up" period lasted 30 to 45 minutes, and, because of the stiffness, physical therapy and other activities were very difficult. She was placed on histamine and noted immediate and marked relief from stiffness. She eventually returned to teaching and for two years has given herself an injection of histamine before arising in the morning. The drug decreases stiffness and pain in this individual to such an extent that without it she can do much less than when she takes the injections regularly.

#### SUMMARY

Histamine diphosphate dilution (1-1000), when properly given to individuals without complete ankylosis of the joints, will increase motility and frequently relieve pain. The subcutaneous administration of the drug seems to be as satisfactory as iontophoresis and is far superior to the use of the ointment in our hands.

Histamine will not cure arthritis. It is at best an adjunct to other forms of therapy and, as such, may be expected to aid in some cases and to fail in others. When such failures are encountered, the drug should be immediately discontinued.

The drug should be administered cautiously to avoid severe reactions. In our experience no shock has been encountered which necessitated treatment. There seems to be no cumulative or deleterious effect from the drug. There was no alteration in blood chemistry, blood pressure, red blood cell count, etc., from the levels determined at the onset of therapy.

Since patients do not readily develop a tolerance for the drug, it can be administered over long periods of time.

Histamine, although not having a specific therapeutic effect in rheumatoid arthritis, when given subcutaneously does seem to be of value in the symptomatic treatment of the disease. It apparently enhances the value of other forms of therapy and, in many instances, enables the patient to carry on activities which would otherwise be impossible.

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## SUBACUTE BACTERIAL ENDOCARDITIS IN OLDER PEOPLE \*

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THE occurrence of a specific disease may vary, not only in the incidence with which it afflicts a number of individuals, but also in the relative number of individuals differing by age, sex, or other factors. How much middle life or late maturity may alter the reaction of the individual to the same disease is a question not entirely clear. It is becoming a more important one in view of the aging of the population and the greater number of older people incurring acute infectious as well as chronic degenerative diseases. In disease of the cardiovascular system, this age variation is most pronounced.

Types of disease that involve the young heart may be entirely different from those afflicting the older heart. Arteriosclerotic disease of the heart seldom develops in young individuals. Acute rheumatic carditis or endocarditis is almost never found in the very old. Differences in the reaction of normal young and normal old hearts to similar physiological conditions have only recently been investigated. Differences in the effect on the young and the senescent heart, of unusual physiological conditions or of disease have been seldom defined. If differences are present, they may be, as Cohn <sup>1</sup> has remarked, striking; for instance, compensation for cardiac defect by hypertrophy is a form of repair incomplete or deficient in old age.

One method for analyzing such differences is the consideration of the effects of a disease that attacks both old and young hearts. Subacute bacterial endocarditis, because of its association with rheumatic heart disease, has been considered an affliction chiefly of younger individuals. Though it will probably remain an illness largely of adolescents and young adults, its more frequent occurrence in older subjects may be expected. Arteriosclerosis, hypertension, and syphilis may, like rheumatic fever, damage the valvular tissue and provide a suitable basis for vegetative endocarditis. If the lives of patients with rheumatic heart disease should be prolonged by increasingly efficient care, the complication of subacute bacterial endocarditis may be postponed to their later years.

This study concerns the appearance of subacute bacterial endocarditis in a number of patients over 40 years of age. The information obtained has been clinical and anatomical.

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Reported in the clinical session of the American College of Physicians at Bellevue Hospital, April 8, 1938.

## METHOD

Clinical and pathological information has been obtained on 28 patients over 40 years of age, observed on the Third (New York University) Medical Division of Bellevue Hospital, from October 1931, to January 1938. Only those cases with diagnosis established by necropsy have been considered; some were under personal observation, the records of others were analyzed. The oldest subjects were 70 and 72 years of age, of whom there were two, both women. Of the 28, 23 were men. In 14 cases the correct antemortem diagnosis was made. During the same period, according to the clinical observations, 25 patients, under 40 and over 12 years of age,\* succumbed to subacute bacterial endocarditis. On 12, necropsy was permitted and the premortem diagnosis confirmed. From the records of this service it appears that subacute bacterial endocarditis has been correctly diagnosed in those under 40, and not sufficiently considered in those over 40 (figure 1). In addition it should be pointed out that of the group

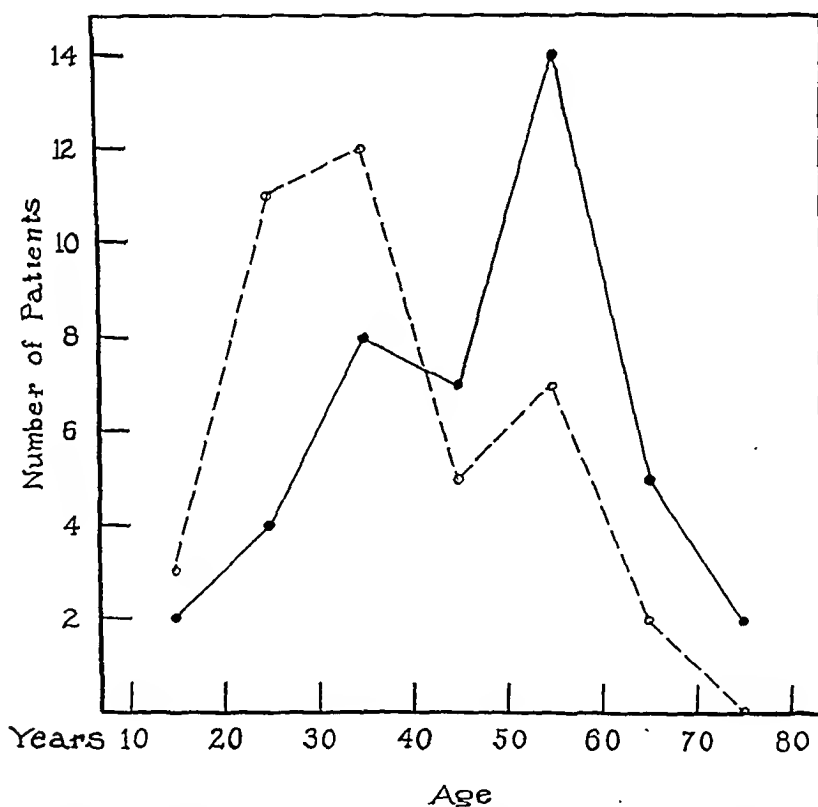


FIG. 1. Subacute bacterial endocarditis. Patients on the Third Medical Division, Bellevue Hospital, October 1931 to January 1938. These curves show the distribution in different decades of life, according to the clinical diagnosis (broken line ----), and according to the anatomical diagnosis (uninterrupted line —). See text for comment.

over 40 the average age of the correctly diagnosed was 51 years, and of the undiagnosed, 59 years.

\* Patients under twelve are not admitted to this service. According to other experience, subacute bacterial endocarditis seldom afflicts individuals before the second decade.<sup>5, 8</sup>

## CLINICAL OBSERVATIONS

As has been remarked, of the 28 patients, 14 cases or one-half were correctly diagnosed clinically, as examples of subacute bacterial endocarditis; the other 14 were not. It is fair to state, however, that in the incorrectly diagnosed group, subacute bacterial endocarditis was often suggested in the differential diagnosis, but the clinical signs and symptoms and the laboratory findings did not confirm this unequivocally as the final clinical diagnosis, and hence it was not made. With two major exceptions, the symptoms and the physical findings were similar in the two groups; all but two had signs of heart disease, all but two had signs of infection. In the group with correct diagnoses cultures of the blood were positive, or embolic phenomena such as petechiae, so indicative of endocarditis in the course of heart disease, were present. In the group without correct diagnoses, complications in other organs, secondary to the endocarditis, were interpreted as the primary disease. In the 14 cases in which the clinical diagnosis of subacute bacterial endocarditis was not made, the final diagnosis at the bedside was: in four, rheumatic heart disease; in four, malignant disease of the kidney; in two, chronic diffuse glomerular nephritis; in one each, luetic and hypertensive heart disease, luetic heart disease, hypertensive and arteriosclerotic heart disease, and streptococcus bacteremia of unknown origin.

One may observe from this tabulation that the differential diagnosis involves primarily either rheumatic heart disease, because of cardiac involvement and infection, or renal disease, because of hematuria. If the events of an incorrectly diagnosed illness are viewed in retrospect, one will find the usual known features of subacute bacterial endocarditis, as follows:

*Case 1.* A 69-year-old male complained of dyspnea, fatigue and epigastric distress on admission to the hospital. Three months previously he had suffered a cold and an attack of severe precordial pain. In the three following weeks, edema of the ankles and dyspnea were present. Thereafter the cardiac reserve gradually declined.

The patient was undernourished, pale and elderly in appearance. The rectal temperature was 100.8° F. The heart appeared enlarged; a systolic murmur was heard at the base and at the apex. The pulse rate was 90 per minute; the systolic blood pressure was 154 mm. Hg, the diastolic 70. Râles were heard at the bases of the lungs, and there was edema of the ankles. The count of the red blood cells was 3.36 million per cu. mm.; that of the white cells 6,300. A few red cells were present in the urine. During the remaining 90 days of life, the temperature varied from normal to 103°. The hematuria was variable, apparent sometimes on gross, at other times on microscopic examination. The count of the red cells in the blood fell to 1.7 million; by transfusion and diet it was increased to 2.2 million. The chemical constituents of the blood were normal. Blood pressure was usually 124 systolic, 48 diastolic. Digitalization had no effect on the congestive heart failure. A yellowish tint developed in the skin; the icteric index was normal. Repeated cultures of the blood were negative. The patient gradually failed, becoming comatose before death. At necropsy, the principal findings were lobular pneumonia, and subacute bacterial vegetative endocarditis of the aortic and mitral valves (figure 2). The leaflets of these valves showed moderate sclerotic thickening of the borders. The heart weighed 420 grams. The spleen was enlarged, weighing 390 grams. The kidneys were normal except for some tubular hemorrhage. There was acute, focal suppurative prostatitis.

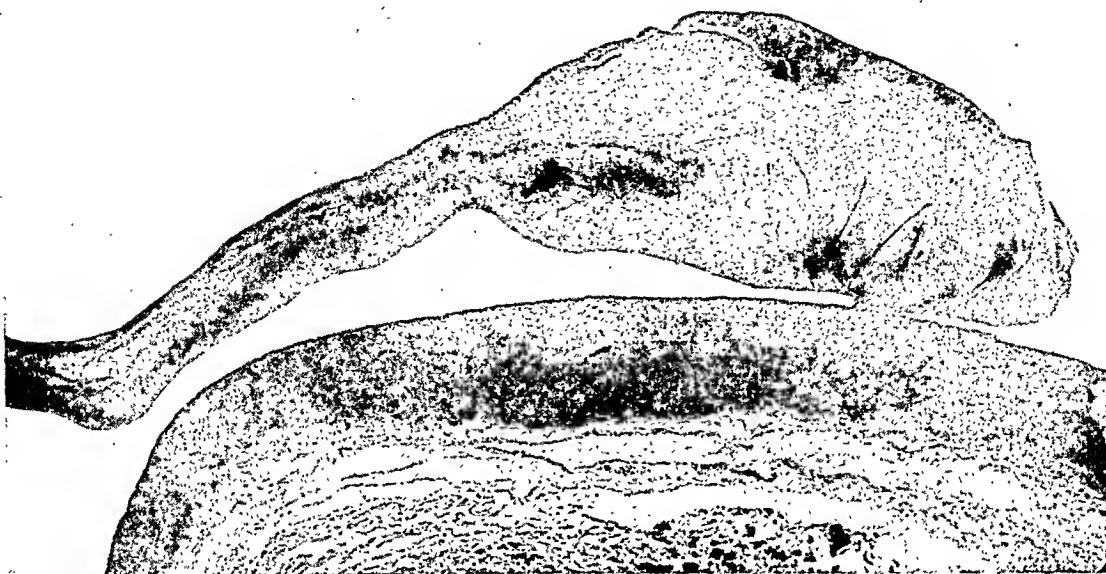


FIG. 2. Subacute bacterial endocarditis and arteriosclerotic heart disease. Section from a leaflet of the mitral valve of a man, aged 69 years (Case 1). The distal portion of the leaflet is thickened and had undergone sclerotic changes with fibrosis and deposition of cholesterol crystals. On the upper border is a vegetation composed of fibrino-purulent exudate, partly organized and containing bacteria. No anatomical evidence of rheumatic infection was found.

The features presented by the illness in this patient are similar to those in Case 2, in which the diagnosis was rendered obvious by the positive blood culture.

*Case 2.* A 50-year-old Italian waiter was admitted with the complaints of progressive weakness of three and a half months' duration, of increasing edema of the feet of seven weeks' duration, and of "red spots" in the skin of five weeks' duration. Three attacks of epistaxis occurred in the preceding ten days. There was no knowledge of hypertension or of lues, or of manifestations of the rheumatic state.

He was dyspneic and orthopneic. Petechial hemorrhages were present in the conjunctival sacs. The heart, with a diffuse and heaving apical impulse, was enlarged; there were a harsh, blowing apical systolic murmur, and a blowing basal systolic murmur; the rhythm was regular. The systolic blood pressure was 100 mm. Hg, diastolic 68. The liver edge was felt two fingers' breadth below the right costal border, and the spleen was just palpable. There were old and recent purpuric hemorrhages over the legs and thighs.

The urinalysis revealed consistently a few red blood cells. The count of the red blood cells ranged from 2.0 to 2.5 million per cu. mm.; that of the white cells from 8,000 to 11,000. The chemical constituents of the blood were normal; the Wassermann reaction was positive. The sedimentation rate of the erythrocytes was normal. The electrocardiographic studies revealed left deviation of the electrical axis with A-V nodal tachycardia, and the teleroentgenogram showed enlargement of the heart. Three blood cultures were positive for *Streptococcus viridans*.

While on the ward, the patient's temperature varied between 101° and 103°. Numerous petechiae appeared from day to day. Digitalization did not affect the congestive heart failure, and the patient became more cachectic and died after 22 days in the hospital, five months after the onset of symptoms.



The necropsy revealed subacute vegetative endocarditis of the tricuspid, mitral and aortic valves. From the vegetations *Streptococcus viridans* organisms were cultured. Sclerosis of the valves, due to degenerative (non-infectious) changes was confirmed by microscopic study. There were infarcts in the kidneys and spleen, and histologic study confirmed the diagnosis of focal embolic glomerulo-nephritis. There was generalized anasarca of the serous sacs and lower extremities.

### CORRELATION OF CLINICAL AND PATHOLOGICAL FINDINGS

Clinical findings and their verification by necropsy \* may be considered on the basis of general symptoms of infection, involvement of the heart, hematological effects, and peripheral effects.

*A. Symptoms of Infection:* The major complaints were usually lassitude, weakness, feverish and chilly sensations, and headache—symptoms commonly associated with febrile illness. Signs of infection were manifested in 26 of 28 patients; the appearance was febrile, the temperature was elevated, the skin was cold and clammy, or warm and moist, and the face was flushed or pale. In 12, signs of infection in the heart were manifested by tachycardia, changing murmurs, and by exclusion of involvement in other organs. In five, the signs and symptoms of systemic infection could not be localized:

*Comment from necropsy:* Infectious endocarditis was present in all of the 28 cases.

*B. Involvement of Heart:* Clinical indications of heart disease were present in all but one of the patients. The antemortem diagnosis of rheumatic heart disease was made in 10, of arteriosclerotic heart disease in two, of luetic heart disease in four, and, in one each, of luetic and hypertensive heart disease, arteriosclerotic and hypertensive heart disease, and arteriosclerotic and luetic heart disease. In nine the underlying heart disease was unknown in type or not recognized. Congenital bicuspid aortic valve was not mentioned.

*Comment from necropsy:* The cardiac lesions were the result of:

Anatomical Heart Disease	Number	Age	
		Average	Range
Rheumatic . . . . .	16 (57%)	53 yrs.	42 to 70 yrs.
Arteriosclerotic . . . . .	7 (25%)	62 yrs.	50 to 72 yrs.
Luetic . . . . .	2 (7%)	52 yrs.	47 and 58 yrs.
Congenital bicuspid aortic valve . . . . .	3 (11%)	55 yrs.	48 to 69 yrs.

1. A murmur or murmurs were found in all patients. A systolic murmur was noted at the apex in 27; it was noted at the base in 19, and always in conjunction with a systolic murmur at the apex. A diastolic murmur was

\* Dr. Eugene Clark, Assistant Pathologist, Bellevue Hospital, kindly advised us in the review of the pathological material.

noted at the apex in 11, and at the base in 15, of whom eight also presented the apical finding. A thrill was observed less frequently; it was felt during systole in six and during diastole in four.

*Comment from necropsy:* Endocardial vegetations were present as follows:

- in 9 on the aortic and mitral valves;
- in 8 on the mitral valve only;
- in 7 on the aortic valve only;
- in 2 on the aortic and tricuspid valves;
- in 2 on the aortic, mitral and tricuspid valves.

All but one of the vegetations occurred on valves deformed by one of the aforementioned predisposing conditions; in the exception the vegetation developed on the mitral valve in a heart with congenital bicuspid aortic deformity.

2. Enlargement of the heart was noted clinically in 27 patients.

*Comment from necropsy:* In 24, the weight of the heart indicated hypertrophy. The mean weight was 571 grams; the greatest weight 1,080 grams in a male patient with longstanding syphilitic heart disease.

3. Electrocardiograms were obtained on 24 patients. In 20 the rhythm was normal, but eight of these had tachycardia. In one, aged 42, with known rheumatic heart disease for 32 years and marked rheumatic mitral deformity, auricular fibrillation had been present throughout the observation in the hospital and for nine months previously; although three blood cultures showed no growth, the diagnosis of subacute bacterial endocarditis was correctly made on the basis of splenomegaly, typical petechiae in the skin and conjunctival sacs, and the febrile course. Another case of advanced rheumatic mitral disease with established auricular fibrillation and subacute bacterial endocarditis has been reported from this clinic.<sup>2</sup> In another, aged 62, with hypertensive and arteriosclerotic heart disease, auricular fibrillation developed during the last few days of life. In two, nodal rhythm was present.

4. Congestive failure developed in 25—being present in 15 for more than four weeks, and in 10 shortly before death. The longest duration of failure was seven months. The average length of congestive heart failure was three and one-half weeks in the group of correctly diagnosed cases, and nearly twice that, or six weeks, in the 14 cases which did not receive a correct clinical diagnosis. Of 15 who received digitalis in adequate therapeutic amounts, therapeutic response did not occur in 12, and occurred only moderately in three.

#### *C. Hematological Effects:*

1. The blood count revealed an anemia in all patients, ranging from 1.9 million to 4.7 million red cells. The average red blood count was 3 to 3.4 million. The leukocyte count varied from 5,400 to 38,000; the average was 13,000 to 14,000.

2. Blood cultures were taken on 23 patients. Twelve, or a little over one-half, were positive; in eight the culture gave *Streptococcus viridans*, in two *Streptococcus hemolyticus*, and in two pneumococcus (Types 3 and 7).

*Comment from necropsy:* Postmortem cultures of the valve leaflets were positive in the 12 cases with positive cultures of the blood during life; in addition, *Streptococcus viridans* was cultured from the valves of two, and *Streptococcus hemolyticus* from the valves of six. Twenty (71 per cent) had bacteriological evidence of subacute bacterial endocarditis. No post-mortem cultures were taken on the remainder.

#### D. Peripheral Effects:

1. Petechiae, either in the skin or the mucous membrane, were observed in 15 patients, but only in four of those in the incorrectly diagnosed group. Of the cases in which clubbing was found, six in all, all were diagnosed correctly. Of the 17 cases in which it was reported as missing, 11 were diagnosed incorrectly. In the remaining five, clubbing was not mentioned. The café-au-lait tint of the skin was recognized in six of the twenty-eight.

2. Enlargement of the spleen was recognized in 12 patients, four of whom were among the undiagnosed cases.

*Comment from necropsy:* The spleen was enlarged on postmortem examination in 26 patients; the weight varied from 230 to 1900 grams. There was infarction of the spleen in seventeen.

3. The kidney lesions were manifested clinically by hematuria in 17 or 60.7 per cent, and by renal insufficiency as measured by an increased non-protein nitrogen content of the blood; 11 had definite azotemia, four were borderline in amount of nitrogen retention, ten were within the normal limits, and three were not examined in this chemical fashion. Using either renal insufficiency or hematuria as an index, we find 21, or 75 per cent, with clinical evidence of renal damage. One or both of these signs were present in 10 of the correctly diagnosed and in 11 of the incorrectly diagnosed group.

*Comment from necropsy:* The nephritides as presented by these older patients were often of a dual character. The total lesions are shown:

Pathological Diagnosis	No.	Per cent
Focal embolic glomerulonephritis (alone or combined) . . . . .	12	42.8
Subacute diffuse glomerulonephritis (with focal lesions) . . . . .	1	3.5
Acute diffuse glomerulonephritis (2 with focal lesions) . . . . .	7	25.0
Chronic diffuse glomerulonephritis (2 with focal lesions) . . . . .	3	10.5
Normal kidney . . . . .	10	35.7

} 11 or 39.2 per cent

Of the 12 cases with focal embolic glomerulonephritis, seven had positive blood cultures and six of these were correctly diagnosed as subacute bacterial endocarditis, while five had negative blood cultures and of these three were correctly diagnosed. Acute, subacute and chronic diffuse glomerulonephritis were divided among six cases with negative blood cultures, two with positive blood cultures, and three in which none were taken. Of this group of eleven, eight were correctly diagnosed as having subacute bacterial endocarditis.

## DISCUSSION

Frequent reports have described the clinical, bacteriological and anatomical features of subacute bacterial endocarditis.<sup>3-19</sup> Although Blumer<sup>5</sup> in 1923 considered that the "figures indicate that the disease is a disease of adolescence and young adults" (80 per cent of 317 patients were under 40 years of age), further observations (14) with present and future populations suggest a large and perhaps major incidence after the age of forty.

In the older patients considered here, the absence of positive blood cultures is an experience found, though less frequently, in younger patients. Bacteremia was not demonstrable in 11 (47 per cent) of 23 patients on whom cultures of the blood were taken; this is a higher percentage than observed in a younger group.<sup>17</sup> Embolic phenomena in the central nervous system, occurring in four, were less frequent than in reports regarding younger patients.<sup>8, 11, 19</sup> The frequency (64 per cent) of renal lesions, either focal embolic or diffuse inflammatory, is in accordance with, or less frequent than in other observations considering all ages.<sup>10, 12</sup>

Valvular deformity of rheumatic type occurred in 16 (57 per cent) of these patients, which is similar to the experience in younger groups.<sup>7, 9, 14, 18</sup> Sclerotic deformity of the valves was present in seven (25 per cent). Congenital bicuspid abnormality of the aortic valve was present in three (11 per cent), maintaining the observation<sup>6</sup> that it is a frequent association of subacute bacterial endocarditis. Lewis and Grant<sup>6</sup> observed that "amongst males, reaching adult life, and possessing congenitally bicuspid aortic valves, 23 per cent at least die of active endocarditis." Presumably a certain percentage die before forty.

Disturbances of cardiac rhythm were not frequent in these older patients—no more frequent than in other observations in a group with an average age of thirty-five.<sup>16</sup> Congestive heart failure, however, occurred more often; of the 28, it was present in 15 (53 per cent) for four weeks or longer, in 10 for one week to ten days prior to death; as pointed out above, the undiagnosed cases presented more difficulty in diagnosis because of longer periods of failure. In a predominantly younger group of 103 patients<sup>13</sup> circulatory function was considered excellent in 76, good in 17, and fair in 10; there were no data on eight additional cases.

## SUMMARY

The clinical picture of subacute bacterial endocarditis in individuals over 40 years of age is not as clearly defined as in younger individuals. Of 28 such patients considered in this report, only 14 received correct diagnosis before death. All cases of subacute bacterial endocarditis under the age of 40 which came to necropsy from the same Medical Service had correct clinical diagnoses.

One wonders, therefore, if the clinical picture of subacute bacterial endocarditis is different in older people. The features are essentially the same,

but they are less accentuated. The common or typical events of subacute bacterial endocarditis as seen in younger patients are not obvious in the older group because heart failure and azotemia are more often present. The latter findings are no doubt associated with decreased cardiac and renal reserve because of age. Subacute bacterial endocarditis is not often considered diagnostically in an elderly patient, who may or may not have congestive failure and who does not present signs, symptoms or history of rheumatic heart disease. A large proportion of the patients in this study (12 of 28) had arteriosclerotic or luetic heart disease, or congenital bicuspid aortic valves which formed an underlying basis for endocarditis. The blood culture was not so frequently positive, possibly because of increased immunity or less virulence of the infecting organism.

Otherwise the clinical events, as has been remarked, are essentially the same as in younger patients. All but two of this group had general signs of a febrile illness, and these two were among the undiagnosed cases. In addition, three of this latter group had a temperature course ranging below 100° F. They had signs of heart disease, perhaps with, perhaps without previous cardiac symptoms, but manifested by enlargement of the heart, by cardiac murmurs, changing or constant in character, and often associated with heart failure, progressive but often mild. Also, complications of moderate secondary anemia, moderate leukocytosis, frequently hematuria and azotemia, enlargement of the spleen, and peripheral embolic phenomena were consistently present.

### CONCLUSIONS

1. Clinical and pathological observations on 28 individuals aged 40 to 72 years, who succumbed to subacute bacterial endocarditis, have been reviewed.
2. Subacute bacterial endocarditis in older people is associated with pre-existing or chronic heart disease. The most common (57 per cent) is rheumatic heart disease, but other types of heart disease are also frequent.
3. The clinical features are essentially the same as those in younger patients, but less accentuated. Congestive heart failure and azotemia are more common; demonstrable bacteremia is less common.
4. Subacute bacterial endocarditis occurs more frequently than suspected or heretofore reported in older individuals.

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# CASE REPORTS

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## CASE REPORT OF URINARY OBSTRUCTION DUE TO CRYSTALLINE CONCRETIONS FOLLOWING SULFAPYRIDINE THERAPY IN PNEUMONIA \*

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THIS case report is presented in confirmation of the observation that urinary obstruction may occur during the course of sulfapyridine therapy as a result of the formation of sulfapyridine concretions in the urinary tract. A similar case, which yielded promptly to treatment, has recently been reported by Carroll, Shea and Pike.<sup>1</sup>

Many reports of gross hematuria following the administration of this drug have appeared in the literature. The occurrence of blood in the urine, under these circumstances, was at first ascribed to a "toxic nephritis." Evidence against this is the character of the abnormal urinary findings and the fact that the anuria disappears when the drug is discontinued. The possible significance of the deposition of actual crystalline concretions which result in the gross hematuria and anuria was first suggested by the animal experiments of Gross and his associates,<sup>2</sup> and Antopol and Robinson.<sup>3</sup> Almost simultaneously Southworth and Cooke<sup>4</sup> reported hematuria, nitrogen retention, and oliguria, with abdominal pain resembling renal colic, in patients receiving sulfapyridine therapy. Actual crystalline sulfapyridine and acetyl sulfapyridine concretions in the urinary tract in humans, established by autopsy, were first noted by Snapper et al.<sup>5</sup> in one patient of a series of four cases showing hematuria during sulfapyridine therapy for pneumonia. Tsao, McCracken, et al.<sup>6</sup> followed with a report of one death due to urinary obstruction with crystalline concretions of sulfapyridine and acetyl sulfapyridine demonstrated at autopsy as obstructing the terminal ureteral orifices.

### CASE REPORT

A 70 year old white male was admitted to the University of Michigan Hospital on February 2, 1940 with a history of a chill three days prior to admission. This was followed by profuse sweating, fever, a progressive cough productive of bloody sputum, and pleuritic pain in the left lower chest. The past history revealed an inadequately treated syphilitic infection in 1920, mild "arthritis" of several years' duration, and the removal of a benign cyst of the left kidney in 1928.

On admission the temperature was 103.8 degrees (rectal), pulse 94 per minute, respiratory rate 26 per minute, and blood pressure of 150 mm. of mercury systolic and 70 mm. diastolic. The patient was a well developed and nourished, acutely ill male who appeared to be about the stated age. There was marked facial flushing, excessive perspiration, but no definite cyanosis. The patient was edentulous and the posterior pharynx was hyperemic. Expansion of the chest was limited bilaterally with im-

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paired resonance from the fourth rib downward anteriorly and over both bases posteriorly. In the same areas, tactile fremitus and voice sounds were increased and bronchial breathing was present. Fine moist râles were heard at both bases posteriorly. The heart was not enlarged; the rhythm regular; aortic second sound was slightly accentuated. There was marked abdominal distention and a large, easily reducible umbilical hernia, measuring approximately four by seven centimeters was present. The liver edge was not definitely palpable. Bilateral hydroceles were present. The peripheral arteries were moderately sclerosed.

Chest roentgen-ray, on admission, showed confluent areas of consolidation in both lower lobes of the lungs.

The sputum revealed a Type III pneumococcus reaction by the Neufeld *quellung* method. On admission, the urine was cloudy, acid in reaction, the specific gravity was 1.012 with a 1 + albumin. Microscopic examination revealed no abnormalities. The hemoglobin was 82 per cent (Sahli), the red blood cell count 4.2 million per cubic millimeter, and the white blood cell count 16,100 per cubic millimeter. The differential count showed polymorphonuclear neutrophils 68 per cent, eosinophils 1 per cent, lymphocytes 20 per cent, and monocytes 1 per cent. Stool examination showed 1 + guaiac and 4 + benzidine reaction. Blood Kahn test was negative. Blood culture showed no growth.

Immediately after typing and obtaining blood for a culture, sulfapyridine with equal amounts of sodium bicarbonate was administered orally. An initial dose of 3.0 gm. followed by a 1.0 gm. dosage every four hours thereafter was given. At the same time, following sensitivity tests, Type III antipneumococcus rabbit serum (Lederle) was given intramuscularly. A total dosage of 230,000 units was administered within the first eight hours. The temperature, pulse and respirations became normal 18 hours after admission, and remained so thereafter. The course of the patient's illness was uneventful until the evening of the fifth day of hospitalization at which time he became slightly disoriented. He complained of severe left costo-vertebral angle pain and tenderness. The total amount of sulfapyridine given over the five day period was 33 gm. His fluid intake for the preceding 24 hours was 1625 c.c., whereas the output, over the same period, was 10 + c.c. (The quantity in one specimen was unrecorded, as it was lost with a bowel movement.) At this time the non-protein nitrogen was 40.2 mg. per cent; CO<sub>2</sub> combining power, 48 volumes per cent; and blood sulfapyridine, 15.6 mg. per cent.\* The sulfapyridine was discontinued. Catheterization of the bladder produced 15 c.c. of grossly bloody urine, acid in reaction, and containing many crystals. Sulfapyridine determination on this urine specimen gave 83 mg. per cent (free). Ninety minutes later, catheterization was repeated with the same results, and the bladder was irrigated with warm saline solution. Two hours later, cystoscopy was performed by Dr. William G. Gordon of the Department of Urology. The bladder was found to contain 100 c.c. of clear urine, with small amorphous conglomerations of crystalline material of miliary size at the base of the bladder. Depositions of crystalline masses were also visualized about both ureteral orifices, and crystals were seen protruding from the right orifice. Signs of traumatization with increased redness and slight edema were noted about both orifices. Ureteral catheters were passed to the level of the renal pelvis with ease; 10 c.c. of clear urine were obtained from the right kidney pelvis whereas the left contained 30 c.c. of grossly blood-tinged urine. Sediments of both specimens after centrifuging revealed many red cells, and characteristic crystals; the reaction to litmus was acid. Ureteral catheters were left in place and irrigations were done with 10 c.c. of warm saline solution every two hours for 10 hours. At the end of this time the catheters were removed. Fluids by slow continuous intravenous drip were begun immediately after cystoscopy; the urinary output for the 24 hours following cystoscopy was 1,290

\* Method of E. K. Marshall, Proc. Soc. Exper. Biol. and Med., 1937, xxxvi, 422; sulfanilamide comparator standards.



c.c. Daily urine examinations continued to show a diminishing microscopic hematuria for five days with complete absence thereafter. The blood sulfapyridine level on February 9, 1940 was 1.3 mg. per cent. Non-protein nitrogen on February 12, 1940 was 38.7 mg. per cent. The patient's subsequent course was uneventful.

### SUMMARY

1. A case of Type III pneumonia treated with serum and sulfapyridine is herein reported.

2. Gross hematuria and anuria due to concretions of sulfapyridine were successfully treated by catheterization and irrigation of the ureters.

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### HISTOPLASMOSIS: REPORT OF A CASE \*

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THE fungus infection now known as histoplasmosis, and its causative agent, the *Histoplasma capsulatum*, were first described by Darling in 1906 and 1908.<sup>1, 2</sup> He reported three cases. Since then, single cases of histoplasmosis have been reported by Riley and Watson,<sup>3</sup> Phelps and Mallory,<sup>4</sup> Crumrine and Kessell,<sup>5</sup> and Dodd and Tompkins.<sup>6</sup>

The disease is manifested clinically by moderate fever, emaciation, splenomegaly, hepatomegaly, enlargement of lymph nodes, leukopenia and slight anemia. In only one of the seven cases recorded was an accurate diagnosis made antemortem. Dodd and Tompkins recognized the parasite in the large mononuclear cells (monocytes) of the blood of their patient during life and the diagnosis was confirmed subsequently at necropsy.

On postmortem examination, in addition to the enlargement of the liver, spleen and lymph nodes, areas of necrosis in the liver with cirrhosis, pseudo-granulomata of the lungs and of the small and large intestines and focal necrosis

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in the lymph nodes have been noted. In some instances ulcers of the colon occurred. In all cases, the *Histoplasma capsulatum* was readily demonstrable within the endothelial cells of the small lymph and blood vessels of the spleen, liver, lymph nodes, bone marrow, lungs and intestines.

Extensive studies on the morphological characteristics of the parasite were made by da Rocha-Lima<sup>7</sup> in 1912. He regarded it as closely related to, if not identical with *Cryptococcus farcininosus*, the causative organism of epizootic lymphangitis of horses and other solipeds.

Darling was unable either to cultivate the organism in artificial media or to transmit the disease to experimental animals.

DeMonbreun<sup>8</sup> in 1934 first succeeded in cultivating the parasite. Under appropriate conditions he was able to culture it in the yeast-like form as it appears in the lesions, and as a mycelium. He was also successful in reproducing for the first time the characteristic clinical and pathological features of the disease in monkeys, and determined that the pathogenic phase of the fungus is the yeast-like form. These findings were confirmed by Ciferri and Redaelli.<sup>9</sup> DeMonbreun also showed that the yeast-like form of the fungus is pathogenic for mice and puppies.<sup>8</sup>

In this communication an additional case of histoplasmosis is recorded. The diagnosis was established by the histologic examination of a lymph node which was removed one day before the patient died. The case is of particular interest because there was clinical and pathological evidence of co-existing lymphatic leukemia.

#### CASE REPORT

*History:* W. W. H., a 56-year-old white farmer who had been a resident of Tennessee all his life was admitted to the Vanderbilt University Hospital, August 13, 1938, complaining of severe sore throat. He had been in excellent health until two years previously when he first noticed small lumps in his neck. These persisted without producing symptoms for about one year when enlargement of the nodes in the inguinal and axillary regions developed. These gradually increased to such size that movements of the limbs became painful and occasioned sufficient difficulty to interfere with the patient's farm work. During the eight months preceding hospitalization he experienced steadily increasing weakness, and he lost 50 pounds in weight. For two months before entering the hospital shortness of breath, intermittent swelling of the ankles and nocturia 2 to 3 times a night occurred, and there were occasional bouts of fever. Three weeks before admission swelling and soreness of his throat developed and caused difficulty in swallowing. Six days before admission he began to cough and expectorated tenacious, foul-smelling, blood-tinged sputum.

*Physical examination:* On admission to the hospital, his temperature was 102.4° F., pulse 128, respiratory rate 26 and blood pressure 140 mm. of mercury systolic and 96 mm. diastolic. He appeared stuporous but at times was somewhat irritable and restless. The respirations were of the Cheyne-Stokes type. Moderate amounts of tenacious, blood-tinged, muco-purulent sputum were expectorated. His breath and sputum had the foul odor characteristic of fusospirochetal pulmonary infections. His skin was hot, red, dry, and it appeared sun-tanned. There was little subcutaneous fat.

There was marked enlargement of the auricular, occipital, cervical, submaxillary, supra-clavicular, axillary, epitrochlear, inguinal and popliteal lymph nodes. These nodes were tender, rubbery, and freely movable. Most of them were discrete although a few were matted together. The largest masses of nodes were in the inguinal regions and measured about 10 by 5 by 4 cm. The axillary masses measured about 9 by 7 by 4 cm.

The eyes and ears showed nothing remarkable. The nasal mucosa was reddened, swollen and partly covered with a dry hemorrhagic exudate. Marked pyorrhea alveolaris was present and the teeth were carious. The pharynx and the right tonsillar fossa were reddened and edematous. Several large deep ulcers covered by white exudate were present in the pharynx. The soft palate was tensely swollen. The trachea was in the normal position. The sternal dullness was increased several centimeters on each side. A few medium coarse râles were heard at the base of each lung posteriorly. The heart was normal. Several firm, discrete, round, freely movable painless nodules were present in the subcutaneous tissue of the abdomen. The edge of the spleen was palpable one finger's breadth below the costal margin. The liver edge extended one finger's breadth below the right costal margin. No other abdominal masses were felt. Examination of the genitalia, rectum and extremities revealed nothing noteworthy.

*Laboratory data:* The urine was normal. The red blood cell count was 3,820,000; hemoglobin 11.6 grams; white blood cell count 12,100 with 29 per cent polymorphonuclear neutrophils and 71 per cent lymphocytes (adult type). The red blood cells showed slight anisocytosis and poikilocytosis, but the hemoglobin content appeared to be normal. The platelets were normal in number and appearance. The Kahn test on the blood was negative. A stool specimen contained no blood, but on microscopic examination from 5 to 10 pus cells per high power field were found; no ova or parasites were seen.

A roentgen-ray of the chest showed an enlargement of the lymph nodes at the hilus of the right lung with some infiltration extending out from the hilus into the lung.

Blood agar plates were inoculated with pharyngeal exudate and incubated at 37° C. for one week. No pathogenic organisms were cultivated. Smears of the pharyngeal exudate revealed many fusiform bacilli and spirochetes. Lymphocytes were present in large numbers, but there were very few polymorphonuclear cells.

*Course in hospital:* The clinical impression was that the patient suffered from some form of malignant lymphoma, possibly lymphosarcoma. However, the appearance of the pharynx, the high fever, the character of the cervical lymph nodes and the sputum suggested that fuso-spirochetal infection of the pharynx and lung was also present.

During the patient's stay in the hospital there occurred a daily elevation of the temperature to about 103° F. He became delirious. His throat was irrigated with sodium perborate at frequent intervals. Fowler's solution was applied to the pharynx several times daily. He was given one blood transfusion (500 c.c.) and one intravenous injection of neoarsphenamine (0.45 gm.). A roentgen-ray treatment (400 r units) was administered over the left side of the neck. He developed signs of patchy consolidation in the lower lobes of both lungs and expired August 20, 1938, one week after his admission to the hospital.

The diagnosis of histoplasmosis was not made until two days after death. A biopsy of an axillary lymph node obtained on August 15 proved to be unsatisfactory. A cervical node was removed on August 19, one day before death. The sections which revealed the characteristic parasite were not available for study until August 22.

*Postmortem examination—Gross:* An autopsy was performed two hours post mortem. The body was that of a well-developed, poorly nourished, white male. There was marked enlargement of the auricular, occipital, cervical, submaxillary, supraclavicular, axillary, epitrochlear, inguinal and popliteal lymph nodes. These nodes were soft and discrete and varied in size from about 2 by 2 by 1 cm. to 7 by 4 by 3 cm. The tissue within the capsules of the nodes was soft and very friable. The peritoneal cavity contained no free fluid and the surfaces were free of exudate. No fluid was present in the pleural cavities. The pericardial cavity contained 5 c.c. of clear, straw-colored fluid. The heart weighed 360 grams. No valvular lesions were present. The

right lung weighed 1050 grams, the left lung 530 grams. There was a diffuse pneumonic process throughout the right lung and an abscess 5 cm. in diameter was present near the hilus. The left lung contained several scattered, small areas of consolidation. The liver was enlarged. It weighed 2900 grams. Its surface was smooth and light brown in color. No areas of scarring or necrosis were seen on the cut surface. The spleen was moderately enlarged and weighed 400 grams. The capsule was smooth and the surface was dark purple in color. The pulp was congested and the Malpighian corpuscles were indistinct. The mediastinal, mesenteric and retroperitoneal lymph nodes were enlarged and had the same gross appearance as the superficial nodes. The mesenteric nodes were matted together in a mass weighing 620 grams. The pharyngeal mucosa was the site of several shallow ulcers and its entire surface was of a dirty gray color.

*Microscopic:* Blocks of tissue were fixed in Zenker's fluid with 10 per cent acetic acid and sections were stained with hematoxylin and eosin. Sections of the cervical, axillary, mediastinal, retroperitoneal, mesenteric and inguinal lymph nodes were studied. The capsules of all the nodes were infiltrated and partly destroyed by numerous small round cells. The normal architecture of the nodes was distorted by the presence of densely packed small lymphocytes. Areas consisting of large mononuclear cells with small nuclei surrounded by abundant pink-staining cytoplasm were present at various points. Within the cytoplasm of these cells were numerous, small, oval or rounded bodies 0.5 to 2 micra in diameter surrounded by refractile non-staining capsules. Usually one or two small masses of dark staining chromatic material were present within the capsule. In the areas of the nodes where the mononuclear cells contained these bodies in greatest abundance there were numerous necrotic foci. Occasional isolated mononuclear cells filled with parasites were scattered throughout the sections. The encapsulated structures within the cytoplasm of the mononuclear cells conformed in every respect to the description given by Darling, DeMonbreun and others of *Histoplasma capsulatum*.

Beside the lesion produced by the parasite the lymph nodes were involved by a process morphologically identical with chronic lymphatic leukemia.

The base of the pharyngeal ulcers consisted of necrotic tissue, fibrin, polymorphonuclear leukocytes, small round cells and masses which appeared to be bacteria. Numerous large mononuclear cells containing the typical parasites of histoplasmosis were present in the submucosa underlying the ulcers and also in the submucosa underlying the intact epithelium. Similar cells containing parasites also infiltrated the adjacent striated muscle. Within the center of dense collections of these cells foci of necrosis were present. There was no ulceration of the epithelium of the epiglottis but the sub-epithelial layer was infiltrated with mononuclear cells, many of which contained parasites.

A diffuse bronchopneumonia with abscess formation was present. Stained smears from the pulmonary exudate contained fuso-spirochetal organisms. *Staphylococcus aureus* was isolated by culture. The spleen and liver showed evidence of chronic lymphatic leukemia but no evidence of parasitic invasion. The adrenals and kidneys were infiltrated with small lymphocytes. No parasites were found within the bone marrow but evidence of chronic lymphatic leukemia was present.

Forty-eight hours after autopsy attempts were made to culture *Histoplasma capsulatum* from the lymph nodes, liver and spleen. The methods described by DeMonbreun<sup>8</sup> were employed. The only organisms recovered were considered to be postmortem contaminants. *Histoplasma capsulatum* was not obtained.

## DISCUSSION

The possibility of a fungus infection of the pharynx was considered ante mortem. Cultures on blood agar plates yielded no pathogenic organism. Blood

smears did not reveal the presence of parasites in the leukocytes. The correct diagnosis was not established until two days post mortem when the sections of the lymph node removed during life became available for study. *Histoplasma capsulatum* was promptly recognized, and this led to the delayed and unsuccessful attempts to cultivate the organism from portions of the liver, spleen and lymph nodes.

Microscopic examination showed the *Histoplasma capsulatum* to be present in many lymph nodes in our case, but none were found in the spleen, liver, bone marrow or lungs. The presence of the parasite in the pharynx and epiglottis of our case is noteworthy. Infection in these locations has not been observed in the other cases reported.

Chronic lymphatic leukemia was apparently the primary disease in our patient. The infection with *Histoplasma capsulatum* appears to have been coincidental. In the case reported by Phelps and Mallory<sup>4</sup> histoplasmosis was encountered as a complication in a patient with cirrhosis of the liver and primary liver cell carcinoma. In the remainder of the cases reported, histoplasmosis was the main disease found at autopsy. As in the previously reported instances of this disease no source of the infection could be determined in our patient. This is the second instance of histoplasmosis reported from Tennessee. The case of Dodd and Tompkins<sup>6</sup> was also reported from the Vanderbilt University Hospital and their patient was a resident of this state. It is interesting in this connection that DeMonbreun<sup>10</sup> has recently observed histoplasmosis in a dog in this region.

### SUMMARY

A case of histoplasmosis associated with chronic lymphatic leukemia is recorded. This represents the second case of histoplasmosis reported from Tennessee. The diagnosis of histoplasmosis was made by the microscopic examination of a cervical lymph node obtained by biopsy. Postmortem examination revealed an extensive infection with *Histoplasma capsulatum* in the pharynx, larynx and lymph nodes in association with the pathological changes of chronic lymphatic leukemia.

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## SIMMONDS' DISEASE (PITUITARY CACHEXIA); REPORT OF A CASE\*

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SIMMONDS' disease or pituitary cachexia is a syndrome ascribed to destruction or physiological exhaustion of the hypophysis (chiefly the anterior portion). The destruction may be caused by embolic infarction, tumor, syphilis, tuberculosis, metastatic abscesses, inflammation, etc. Clinically the Simmonds' syndrome is characterized by cachexia, premature senility, atrophy of the gonads and genitalia, with amenorrhea, atrophy of the breasts, loss of pubic and axillary hair, loss of libido, integumental changes (chiefly dryness of the skin), anorexia and constipation, hypotension and muscular weakness, hypoglycemia, decreased sugar tolerance, lowered basal metabolism and depressed specific dynamic action of proteins, anemia, lymphocytosis and sometimes eosinophilia. These symptoms are believed to be due to the deficiency or absence of the various hormones elaborated by the anterior hypophysis especially the thyrotropic, adrenotropic and gonadotropic hormones.

Since Simmonds' original report<sup>1</sup> of the disease entity which bears his name, approximately 100 reputed cases have been published. Postmortem examinations were not reported in many of these cases, so that confirmation of the pathogenesis was not always satisfactory. In more recent years successful replacement therapy has been reported in a few instances. Having observed for two years a patient on whom a clinical diagnosis of pituitary cachexia was established and on whom subsequently a postmortem examination verified the diagnosis it would seem justifiable to add the case to the literature.

Adequate compilations and bibliographic reviews of Simmonds' disease have appeared in the American and German literature in the past few years. In lieu of repetition attention is directed toward the readily available papers of Silver,<sup>2</sup> Calder,<sup>3</sup> and Graubner.<sup>4</sup>

### CASE REPORT

J. B., white, unmarried female, aged 20, of Scotch ancestry, oldest of six siblings, was perfectly well until the age of 14 years, when she noticed difficulty in seeing the blackboard in school. The disturbance in vision increased during the following two years until she could discern only large objects. She also noted difficulty in walking because of frequent stumbling. She was taken to a hospital where a diagnosis of an intracranial lesion was made (pituitary tumor suspected), and seven treatments with deep roentgen-ray were given. These treatments were followed by severe frontal

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headaches. Vision rapidly failed and when seen two and a half years later the patient was totally blind. At this time it was learned that the patient had never menstruated, and had lost 40 pounds (119 to 79) since the onset of the illness. Physical examination revealed an underdeveloped, emaciated girl of 18 years who appeared several years older than the stated age (figure 1). She was nervous, irritable, and rather childish in behavior. There was no light perception in either eye. Due to the blindness a constant "searching type" of nystagmus had developed in each eye. The skin was dry, the scalp hair coarse. There was absence of axillary and pubic hair, and the breasts were barely outlined. The heart, lungs and abdomen were normal. Blood pressure was 80 mm. of mercury systolic and 60 mm. diastolic. The genitalia were infantile.

1928

1934



FIG. 1. Photographs of patient in 1928 at age 14 (weight 120 lb.) and in 1934 at age 20 (weight 60 lb.). Note the extreme emaciation characteristic of pituitary cachexia.

Neurological examination showed all the cranial nerves except the optic nerves to be intact. There was generalized muscular weakness of all extremities but no ataxia or paralysis. There were no disturbances of sensory pathways. Reflexes were somewhat hyperactive, but no pathological reflexes were elicited. Anthropometric studies were normal.

Laboratory, roentgen-ray, and special studies were as follows: Blood chemistry: urea 11, 16 mg. per cent; uric acid 3.0, 4.3, 5.0 mg. per cent; creatinine 1.3 mg. per cent; sodium chloride 540 mg. per cent; calcium 10.5 mg. per cent.; inorganic phosphorus 4.6 mg. per cent;  $\text{CO}_2$  combining power 59, 60, 67, vols. per cent; cholesterol 68, 72 mg. per cent; sugar 48, 86, 73, 91 mg. per cent. Glucose tolerance test (venous blood), fasting 48 mg. per cent, first hour 147 mg. per cent, second hour 158 mg. per cent. Eleven 24-hour specimens of urine varied in volume from 95 c.c. to 590 c.c. Sodium chloride excretion in three 24-hour collections was 1.05, 0.88, 1.06 gm. Ten single samples of urine showed no abnormalities. The intracutaneous tuberculin test (1:

1000 O.T.) was positive. Gastric contents contained free hydrochloric acid. The Wassermann and Kahn tests were negative. Spinal fluid was clear, contained three cells per cu. mm.; Pandy test was negative; no tubercle bacilli could be isolated. No parasites or ova were found on examination of the feces. Serial blood counts (table 1) showed a normochromic anemia, progressive in character, and a transient relative lymphocytosis. Blood platelets were 210,000 per cu. mm., bleeding time was eight minutes, clotting time five minutes, clot retraction was normal.

TABLE I  
Serial Blood Counts of Patient J. B.

Date	Hb. Sahli	R.B.C.	C.I.	W.B.C.	Polymorpho-nuclears		Eo-sino-phil	Baso-phil	Lympho-cytes	Mono-cytes
					Seg-mented	Non-Seg-mented				
1/26/33	73	4,110,000	0.9	5,500	38	7	2	2	47	4
7/20/33	70	3,530,000	0.9	5,500	43	5	4	1	44	3
1/15/34	76	3,790,000	1.0	6,600	48	10	2	2	33	5
4/ 6/34	65	3,020,000	1.0	7,400	51	10	1	1	33	4
6/ 6/34	55	2,650,000	1.0	4,600	38	17	0	0	31	8

Seven separate determinations of the basal metabolic rate varied from minus 25 to minus 41. The specific dynamic action of proteins (Gordon technic) was depressed, showing a change from minus 35 to minus 23 following the protein (difference 12). The control patient showed a change from minus 13 to plus 22 (difference 35) following a similar meal.

The Goetsch adrenalin test was rather striking. Following the injection of 1 c.c. of adrenalin there was an initial rise in systolic blood pressure from 76 to 116 mm. Hg and of the pulse rate from 96 to 132. Both dropped very slowly, not returning to normal until two hours had elapsed. This was in marked contrast with the control patient whose systolic blood pressure and pulse rate returned to normal in nine and five minutes respectively.

Serial roentgenograms of the sella turcica (figure 2) showed progressive enlargement. In July 1930, on a film taken at 30 inches, the sella measured 1.65 cm. in width and 1.3 cm. in depth. There was no erosion of the floor or clinoid processes. In January 1933 the sella measured 1.8 cm. in width and 1.6 cm. in depth. The dorsum sellae appeared thinned, the clinoid processes showed some absorption, and the sella was deeper and wider, the floor of the sella being depressed upon the sphenoidal sinus. In January 1934 the sella measured 2.25 cm. in width and 1.6 cm. in depth. There appeared to be extension of the process anteriorly, producing more widening. In April 1933 roentgenograms of the long bones and spine showed marked osteoporosis but no cystic areas. The epiphyseal lines of the long bones were united, whereas those of the scapulae and clavicles were not. A flat roentgen-ray film of the abdomen showed no evidence of calculi in the kidney regions. Roentgenograms of the chest showed nothing of interest.

Examination of the optic fundi (Drs. Koenig and Freeman) showed bilateral complete optic nerve atrophy, but no evidence of increased intracranial pressure. Examination of the mouth (Dr. S. Koepf) revealed no dental lesions that could be attributed to the pituitary condition. There was no atrophy or hypoplasia of the teeth. Cuspal formation was normal in respect to spacing and height. The clinical diagnosis was Simmonds' disease due to destruction of the pituitary gland by a tumor.



## ROENTGEN-RAY OF SELLA TURCICA



FIG. 2. Roentgen-Ray pictures of the sella turcica showing progressive enlargement caused by the growth of the pituitary tumor.

The clinical course was progressively downhill. The patient was drowsy and slept during the greater part of the day. At times it was necessary to arouse her for meals. She had marked anorexia and frequently refused to eat. However, she was inordinately fond of candy. There was a further loss of weight to 55 pounds. Body temperature ranged from 94° to 98° F., pulse rate from 70 to 80 per minute. The patient's general condition was considered too poor to permit surgery. Replacement therapy with anterior pituitary substance was instituted. Fifty-seven daily parenteral injections of pituitary extract freshly prepared by Professor C. G. MacArthur were given. Results were unsatisfactory. Finally, as a last resort, surgical exploration (Dr. Hamby) of the intracranial cavity was attempted and a tumor was located in the hypophyseal region. The tumor appeared cystic in character and aspiration revealed a gelatinous, sanguineous content. Attempt at removal of the tumor was considered inadvisable. The patient expired two days later. Autopsy was performed by Dr. W. F. Jacobs.

#### AUTOPSY PROTOCOL

The body is that of a very slender, emaciated, white female, very pale and anemic in appearance. The external genitalia are infantile, the pubic and axillary hair are absent. The breasts are barely indicated. After removal of the calvarium, the right cerebral hemisphere appears partly collapsed with small fragments of blood clot over the dura which is found incised. After freeing and separating the dura, the convolutions of the cerebral hemispheres, which are markedly flattened, are removed, revealing a multicystic tumor (figure 3) presenting along the incision line, bulging upward chiefly on the right side, but extending definitely to the left of the midline, the cerebral substance being compressed and pushed outward. The under surface of the removed portion reveals circumscribed areas of necrosis with the tumor path upward. The tumor is flaccid and collapsed in part, lying between the temporal lobes and extending forward to a line crossing the tips. Posteriorly it extends to a line limited by the pons. The lateral dimensions of the tumor mass are 4 cm. On its cut surface it measures 4.5 cm. in the anteroposterior and superior inferior aspects. The tumor weighs 82 grams. The cut surface of the tumor reveals a thickened capsule with one large tenacious cavity containing reddish-brown material partly fixed by formalin. Two small pockets measuring 8 by 10 mm. are revealed along the uppermost edge. The contents of these two pockets are gelatinoid. The dura covering the tips of the petrous temporal bone blend with the tumor capsule. The sella turcica is found to be expanded in all directions, thin and partly eroded. Anteriorly it measures 3 cm. and laterally 3 cm. The pituitary is of tissue paper thinness, small, flattened and compressed, lying contiguous with the capsule of the tumor. On separating the bony fragments of the cranial floor from the cystic tumor, the dura found covering the tumor is blended with the dural covering of the sphenoid. The pineal glands appeared slightly larger than usual.

The heart, lungs, liver, pancreas, spleen, kidneys, adrenals, ovaries, Fallopian tubes, and uterus all reveal normal configuration and relations, but are all hypoplastic and remarkably small in size (microsplanchnia). The formalin fixed organs, wiped dry and weighed 24 hours after the autopsy, are as follows: The combined weight of the lungs is 394 grams, the heart 144 grams, the pancreas 64 grams, the spleen 46 grams, the stomach and duodenum 160 grams, the liver 290 grams, the ovaries, tubes and uterus combined 15 grams, the right kidney 43 grams, the left kidney 43 grams, the thyroid 9.6 grams, the pineal bodies 0.4 grams, the adrenals 4 grams.

#### HISTOLOGY

Sections of the tumor reveal cysts as is apparent on gross examination with a hand lens. These cysts are lined by epithelial cells, with elongated cytoplasmic proc-

esses. These cyst cell collections at times suggest the picture of an adamantinoma, with the epithelial cells to the periphery and a delicate central reticulum of connective tissue. In none of the tumor sections is keratinization present. Most frequently the cystic areas are large, with an accumulation of fine granular debris, and the epithelial cell element is reduced to a single layer of irregular squamous cells, at times separated from a basement zone of reticulum cells. Some of the larger cysts are confluent. The



FIG. 3. Photograph of the gross specimen of the cystic pituitary tumor.

bulk of the stroma exhibits smooth muscle fibers and connective tissue, irregularly arranged. Within the meshes are ganglion cell-like structures; these are few and scattered. Also scattered and comparatively few in number are minute duct-like structures lined by a single layer of cells, a homogeneous eosin stained content and a clear zone to the outer side. In this stroma of connective tissue there are a few intervening patches of an embryonic form of connective tissue. There are fairly well defined arteries, arterioles, and capillaries.

The extrasellar location of the tumor and its relation to the pituitary, the epi-

thelial lined cystic cavities, the epithelial cell rests, and the absence of metastasis and infiltrative extension mark it as a histologically benign pituitary stalk tumor.<sup>5</sup>

On section of the remains of the hypophysis no abnormality is noted; the cells are well differentiated and proportioned. The abdominal thoracic organs on routine histological study do not reveal any features of unusual interest. There is moderate hyaline degeneration of the arteries of the heart muscle. The adrenals are normal. Section of the pancreas reveals an accumulation of zymogen granules in the gland cells. Sections of the thyroid exhibit large collections of lymphocytes in the stroma, the colloid is homogeneous and evenly stained, the lining cells are low columnar and well defined. The capsules of the kidney are thickened by fibrosis. Anatomical diagnosis: Pituitary stalk tumor (cystic epithelioma); pituitary, optic nerve and cerebral compression; microsplachnia; emaciation; craniotomy.

#### DISCUSSION AND SUMMARY

The significant clinical symptoms and signs were cachexia, blindness, loss of axillary and pubic hair, atrophy of breasts and genitalia, amenorrhea, asthenia, anorexia and constipation, integumental changes, hypotension, hypothermia, oligodipsia, oliguria, mental changes and pathological sleep. Laboratory studies showed a lowered basal metabolic rate, lowered or depressed specific dynamic action of proteins, hypoglycemia, decreased glucose tolerance, hypocholesterolemia, hypochloremia and hypochloruria, anemia and relative lymphocytosis, disturbed water and salt balance. Anthropometric studies did not show any deviation in bony measurements from the normal.

Not all of these abnormalities, of course, are a feature of destruction of the pituitary. It was felt that the mental changes, pathological sleep, hypothermia, disturbances in water and salt balance, and the blindness were probably due to injury by the expanding tumor onto surrounding structures, especially the optic nerves and hypothalamus.

Replacement therapy and exploratory craniotomy were unsuccessful. At autopsy a pituitary stalk tumor (cystic epithelioma) was found. There was generalized microsplachnia of all organs.

The writer wishes to express appreciation to Professor C. G. MacArthur for the pituitary extracts, to Dr. W. F. Jacobs for the autopsy material, and to both for their kind advice and suggestions.

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## EDITORIAL

### *CONTROL OF THE DOSAGE OF ANTIPNEUMOCOCCAL SERUM IN THE TREATMENT OF PNEUMONIA*

Since effective antipneumococcal sera first became available for the treatment of acute lobar pneumonia the need of some precise method for determining the quantity of serum required has been evident. Attempts have been made to estimate this by considering such factors as the day of the disease on which treatment is started, the extent of the lung tissue affected, the presence or absence of bacteremia and the apparent degree of intoxication, as well as the clinical response to treatment. Although these points are of considerable assistance in the absence of more precise standards, experience soon showed that they are not satisfactory and that in individual cases they may be seriously misleading. In some cases, although a fall in temperature, arrest of the process in the lungs and symptomatic improvement seemed to indicate that sufficient antiserum had been administered, the disease has later relapsed and progressed to a fatal termination. In other cases, persistent fever and failure to improve clinically have been found later to be due to focal complications such as empyema, sterile pleural effusions, arthritis or endocarditis, conditions which ordinarily cannot be cured by an excess of serum.

The desirability of giving amounts of serum sufficient to neutralize all of the specific polysaccharide in the tissues is obvious. On the other hand, it is important practically to avoid a gross excess of serum, both because of its high cost and because of its tendency to increase the frequency and exaggerate the intensity of serum disease.

The fact that the effectiveness of antipneumococcal serum is probably due to its antibody content, as measured by its protective power for mice and less precisely by its agglutinin content, led Sabin<sup>1</sup> to utilize the appearance of agglutinins in the patients' blood as an indication that sufficient serum had been administered. It was soon shown that agglutinins may appear before sufficient serum has been administered to bring about recovery. Attempts by Bullova<sup>2</sup> to utilize a quantitative modification of this method, and by Bullova and Sharff<sup>3</sup> to use a modification of Neufeld's "quellung" reaction proved unsatisfactory for the same reason.

Tillet and Francis<sup>4</sup> found that patients convalescent from pneumonia would give a positive skin reaction to the intradermal injection of a minute amount of the highly purified homologous capsular polysaccharide. The

<sup>1</sup> SABIN, A. B.: The microscopic agglutination test in pneumonia; its application to rapid typing and control of serum therapy, *Jr. Infect. Dis.*, 1930, xlv, 469.

<sup>2</sup> BULLOVA, J. G. M.: The management of the pneumonias, 1937, Oxford University Press, New York.

<sup>3</sup> BULLOVA, J. G. M., and SHARFF, J.: Quantitative capsule swelling tests in blood serum of pneumonia patients, *Jr. Infect. Dis.*, 1937, lxi, 55.

<sup>4</sup> TILLET, W. S., and FRANCIS, T., JR.: Cutaneous reactions to the polysaccharides and proteins of pneumococcus in lobar pneumonia, *Jr. Exper. Med.*, 1929, i, 687.

reaction consisted of a wheal and an erythematous flare appearing within 10 to 30 minutes and fading within one to two hours. The reaction did not appear until recovery was under way, and was always associated with the presence of antibodies (agglutinins and protective substances) in the blood. It remained negative in fatal cases, even though antibodies could sometimes be demonstrated in the serum. Francis<sup>5</sup> reported a study of the test in 48 cases of Type I pneumonia treated with antiserum. He regarded it as superior to the agglutination test as a guide to treatment and emphasized the fact that a positive reaction depends not only upon the presence of antibodies in the blood serum, but also upon the reactivity of the skin. The latter is lacking in gravely ill cases running an unfavorable course. "When positive it invariably denotes that recovery has begun, when negative it indicates further serum therapy."

Francis' observations were confirmed by MacLeod, Hoagland and Benson.<sup>6</sup> Finland<sup>7</sup> and Bullova and Sharff,<sup>8</sup> on the other hand, did not find the skin test entirely dependable. More recently, however, Wood<sup>8</sup> has reported a careful study of the test, and its use in 51 cases of pneumonia treated with serum. Serum was given in large doses at short intervals until an unquestionably positive reaction was obtained. It was then stopped, without regard to the clinical condition of the patient. The quantity required varied from 11,000 to 1,983,000 units. Such differences could not have been foreseen or estimated by any rule of thumb. In general, he fully confirms Francis' observations as to the characteristics of the test and as to its value as a guide in prognosis and treatment. Every patient who recovered developed a positive skin test except one case—a negro—in whom it was impossible to make a reading. His observations indicate that the reaction is due to a combination of specific polysaccharide and antibody in the skin. He also found that in severely ill patients the skin may fail to react, even though both substances are present; or that a reaction which has been positive may become negative. In four of five such cases, however, additional serum restored a positive reaction and recovery occurred.

There are some limitations which must be observed in the interpretation of the test. It is essential that the solution of polysaccharide used for testing be pure. Contamination with a trace of protein or other materials is likely to cause nonspecific skin reactions which destroy the value of the test. In five cases, for unknown reasons, a positive skin reaction was obtained early

<sup>5</sup> FRANCIS, T., JR.: The value of the skin test with type specific capsular polysaccharide in the serum treatment of type I pneumococcus pneumonia, *Jr. Exper. Med.*, 1933, lvii, 617.

<sup>6</sup> MACLEOD, C. M., HOAGLAND, C. L., and BENSON, P. B.: The use of the skin test with the type specific polysaccharides in the control of the serum dosage in pneumococcal pneumonia, *Jr. Clin. Invest.*, 1938, xvii, 739.

<sup>7</sup> FINLAND, M.: Adequate dosage in the specific serum treatment of pneumococcus Type I pneumonia, *Am. Jr. Med. Sci.*, 1936, cxlix, 849.

<sup>8</sup> WOOD, W. B.: The control of the dosage of antiserum in the treatment of pneumococcal pneumonia. I. A study of the mechanism of the skin reaction to type specific polysaccharide, *Jr. Clin. Invest.*, 1940, xix, 95.

*IBID.*: II. The clinical application of the Francis skin test, *Jr. Clin. Invest.*, 1940, xix, 105.

in the disease before the serum had been administered and before antibodies were demonstrable in the serum. The procedure is manifestly of no value in such cases, and if it is to be used as a guide to treatment, a negative test must be obtained before any serum is administered. In three cases a positive reaction was present shortly before death. This was owing in one case to pneumococcal meningitis; in one to pneumococcal endocarditis; and in one to uremia, after apparent recovery from the pneumococcal infection. Persistent fever and clinical illness after the skin test became positive usually meant some complicating focal infection, most often an empyema or a sterile pleural effusion, which demands surgical treatment and will not be influenced by further intravenous administration of serum. In one case it was owing to a recurrent pneumonia caused by a different type of organism.

The test also proved satisfactory in eight cases receiving both sulfapyridine and serum.

More work is obviously necessary to determine precisely the limitations of the test. It promises to be of great practical value in that in most cases, at least, it is a dependable guide as to the amount of antipneumococcal serum required, and as to the outlook for recovery. In many cases, also, it may suggest the existence of some focal, complicating infection.

The use of sulfapyridine has greatly restricted the need for serum therapy in pneumonia. There are, however, some patients who can not take sulfapyridine because of its toxicity. In a few cases sulfapyridine is ineffective (Long and Wood).<sup>9</sup> Experience may still show that a combination of serum and sulfapyridine is more effective than either alone. There will remain a definite, if relatively circumscribed, field for the use of serum, and the test is apparently applicable to such cases.

P. C.

<sup>9</sup> LONG, P. H., and WOOD, W. B.: Observations upon the experimental and clinical use of sulfapyridine. II. The treatment of pneumococcal pneumonia with sulfapyridine, *ANN. INT. MED.*, 1939, xiii, 487.

## REVIEWS

*Handbook of Hematology.* In 4 volumes. Vol. 3. Edited by HAL DOWNEY, Professor of Anatomy, Medical School, University of Minnesota, Minneapolis. Thirty-seven contributors. 3136 pages. 1448 illustrations, including 50 colored plates. Paul B. Hoeber, Inc. (Medical Book Department of Harper Brothers), New York. 1938. Price, \$85.00 set. Volume three, pages 1587-2360.

The third volume of the *Handbook of Hematology* contains 13 sections, the contents of which are approximately equally divided between discussions of various hematological disease entities and morphological and pathological data concerning various parts of the hemolytopoietic system. Thus there are chapters on the spleen, hemolymph nodes, bone marrow, the myeloblasts and myeloid metaplasia as well as individual sections on classification of the anemias, aplastic anemia, pernicious anemia, chronic hereditary hemolytic jaundice, sickle cell anemia, and ovalocytosis. The scholarly approach to each subject, noted in previous volumes, is apparent here also. The voluminous bibliographies appended to each chapter are especially worthy of comment since they are extremely helpful to the worker in this field.

The monographic proportions of many of the chapters invite individual comment in some instances. In the section on the spleen the embryology, anatomy, and pathology are exceedingly ably covered, but it appears to the reviewer that a more detailed consideration of the physiologic data with reference to this viscus would have been extremely helpful. The several sections devoted to a consideration of normal and pathological bone marrow structure are a source of information unrivaled in the English or American literature. The existence of the myeloblast, its cytological characteristics, its possible identity with the lymphoblast, and evidence for its being the stem cell for hemocytes arising in the marrow are presented in a very illuminating and beautifully illustrated section by Downey. The reviewer, however, cannot but take exception to some of the views presented in the chapter on classification of anemias. The author presents an etiologic classification in which, for example, the anemia associated with leukemia is placed in a category of "sequelae of toxic conditions." This apparently negates the influence of the hemorrhagic manifestations of many acute leukemias and the myelophthisic process associated so often with chronic leukemia. Nor does it seem rational for a morphological classification to separate various types of anemia on the basis of whether they show anisocytosis or poikilocytosis. The section on pernicious anemia presents many valuable data, but it is rather disappointing to find the neurological aspects of this disease dismissed with only five or six lines of comment.

With the exception of these inadequacies, culled from a volume of approximately eight hundred pages, the bulk of the material gathered together in this volume represents a contribution to the field of hematology which is invaluable.

M. S. S.

*The Compleat Pediatrician.* By W. C. DAVISON, M.D. 250 pages; 24 × 16 cm. Duke University Press, Durham, North Carolina. 1938. Price, \$3.75.

One is perhaps most impressed by the very clever arrangement of "*The Compleat Pediatrician*." Only after a study of the rather simple instructions for its use can the book be fully appreciated.

Its outstanding purpose is its aid in diagnosis, which is accomplished by a grouping of symptoms. The symptoms and diseases have been arranged into seven chapters on the basis of the anatomical system most often involved. Each of the chapters starts



with a list of symptoms and signs involving that particular system, together with a list of the diseases which cause them most frequently.

That "The Compleat Pediatrician" is of value as a quick reference there can be no doubt, since it contains a wealth of information gleaned from extensive investigation of recent literature. Chapters on treatment, medications, laboratory, nutrition, growth and development are also present.

It is the reviewer's opinion that the book is especially useful to the general practitioner as a quick reference, but decidedly less important to one specially trained in pediatrics. Many of the descriptions of diseases must through necessity be so brief that they leave a sensation of thirst that remains unquenched.

W. M. S.

*Proctology for the General Practitioner.* By FREDERICK C. SMITH, M.D., M.S.C., (Med.), F.A.P.S. 386 pages; 23.5 × 15.5 cm. F. A. Davis Company, Philadelphia. 1939. Price, \$4.50.

For the general practitioner with limited time at his disposal, this book affords an opportunity to acquire some knowledge of recent advances and generally accepted principles in proctologic practice. Much shorter than the usual work on the subject, it lays particular stress upon diagnosis and diagnostic methods along with such minor operative procedures as can be performed in the office. Sclerotherapy and injection methods for the relief of symptoms are dealt with adequately and in their true perspective. Anesthetic methods receive more than the usual attention. Operations for hemorrhoids, fissure, fistula are given in detail but the more extensive surgical procedures are only concisely described. The inclusion of a chapter on the commoner intestinal parasites is a welcome feature. The illustrations are largely by the author but he has also used cuts from standard textbooks, wherever they appeared to be helpful. For those who want their information in concentrated form, this book will suffice.

M. E.

*Doctors on Horsback.* By JAMES THOMAS FLEXNER. 359 pages; 22 × 15 cm. The Viking Press, New York. 1937. Price, \$2.75.

Students of American history as well as students of medical history will be equally attracted by this book. The pioneer physicians of America established the medical profession and its institutions, encountered a revolutionary war with all its medical problems, and in addition, made lasting fundamental contributions to medical knowledge. Speaking of the debt owed the pioneers of medicine by the modern physicians, the author in his Foreword says, "—in the settlements of a new nation there appeared doctors of genius, explorers who, without laboratories or instruments of precision or even any formal training, made great discoveries that helped usher in the age of modern medical science. The modern physician, with all his varied resources, follows the trails these half-forgotten pioneers have blazed."

The medical men of the American Revolution are well represented by chronicles of John Morgan and Benjamin Rush. The story of Ephraim McDowell, the "father of ovariectomy," is interestingly told. The first medical student in Cincinnati and later the great physician of the Mississippi Valley was Daniel Drake. His life story as told in this book is most absorbing. The book also contains one of the most romantic stories of pioneer medicine, the story of William Beaumont who became one of the world's greatest physiologists. In the "ether controversy" which continues today, the author suggests an amicable settlement by proposing to give credit to both William T. G. Morton and Crawford W. Long as almost simultaneous discoverers of anesthesia.

Numerous source documents are quoted in which the author has modernized the

spelling and punctuation. The author does not hesitate to lay bare the true state of affairs as revealed by the source material which he searched.

There are an excellent bibliography and index. It is unusual that one finds accurate history told with absorbing interest, and even though written in separate sections the book seems an integrated whole to the absorbed reader.

J. E. S.

*Diagnostic Signs, Reflexes and Syndromes (Standardized)*. By WILLIAM EGBERT ROBERTSON, M.D., F.A.C.P., and HAROLD F. ROBERTSON, B.S., M.D., F.A.C.P. 309 pages; 18 × 12.5 cm. F. A. Davis Company, Philadelphia. 1939. Price, \$3.50.

This book presents a new departure in medical collation. The authors have gathered and codified an amazing number of signs, reflexes, and syndromes. Where confusion existed they trace sources back to authorities and briefly mention pertinent facts. Throughout the compend-size volume are many cross references, no index. The style is pleasantly modern. As far as this reviewer's knowledge goes, no gross misstatements of fact nor departures from usually accepted terminologies are to be found. There is a gratifying freedom from typographical errors. Nightly perusal is recommended to all medical people, because of surprising and little known facts which will be revealed about signs and symptoms of everyday use and interest.

C. A.

## COLLEGE NEWS NOTES

### NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. George C. Griffith, Philadelphia, Pa.  
Dr. Maud L. Menten, Pittsburgh, Pa.

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### GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following books donated to the College Library:

"Graduate Medical Education in the United States: I—Continuation Study for Practicing Physicians, 1937 to 1940" from the Council on Medical Education and Hospitals of the American Medical Association;  
"Dr. Lawrence F. Flick—1856-1938" from the White Haven Sanatorium Association.

The following gifts to the College Library of publications by members are gratefully acknowledged:

#### *Reprints*

Dr. J. G. Archer, F.A.C.P., Greenville, Miss.—2 reprints;  
Dr. J. Edward Berk (Associate), Philadelphia, Pa.—5 reprints;  
Dr. Philip G. C. Bishop (Associate), New York, N. Y.—1 reprint;  
Dr. Belford C. Blaine (Associate), Pottsville, Pa.—"Minutes of the Commission on Diabetes, October 3, 1939";  
Dr. William Ramsey Blue (Associate), Memphis, Tenn.—1 reprint;  
Dr. Leon L. Blum (Associate), Terre Haute, Ind.—5 reprints;  
Dr. Verne S. Caviness, F.A.C.P., Raleigh, N. C.—6 reprints;  
Dr. Walter Clarke, F.A.C.P., Caldwell, N. J.—1 reprint;  
Dr. Samuel Cohen (Associate), Jersey City, N. J.—7 reprints;  
Dr. Frederic G. Dorwart, F.A.C.P., Muskogee, Okla.—1 reprint (in duplicate);  
Dr. Joseph F. Elward (Associate), Washington, D. C.—1 reprint;  
Dr. Robert H. Felix (Associate), Lexington, Ky.—1 reprint;  
Dr. A. Allen Goldbloom, F.A.C.P., New York, N. Y.—1 reprint;  
Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—10th, Second Series, Supplement to "Modern Drug Encyclopedia and Therapeutic Guide";  
Dr. Lynn T. Hall, F.A.C.P., Omaha, Nebr.—2 reprints;  
Dr. Elmer Highberger, Jr. (Associate), Greensburg, Pa.—1 reprint;  
Dr. Clifton K. Himmelsbach (Associate), Lexington, Ky.—1 reprint;  
Dr. Morrill L. Ilsley, F.A.C.P., Claremont, Calif.—1 reprint;  
Dr. William H. Kraemer, F.A.C.P., Wilmington, Del.—1 reprint;  
Dr. Michael Lake, F.A.C.P., New York, N. Y.—5 reprints;  
Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—"Ninth Annual Report of the Tuberculosis Committee, American Student Health Association";  
Major H. P. Marvin, (MC), USA., F.A.C.P., Washington, D. C.—2 reprints;  
Dr. Oliver T. Osborne, F.A.C.P., New Haven, Conn.—1 reprint;

Dr. H.D. Piercy, F.A.C.P., Cleveland, Ohio—1 reprint;  
Dr. B. S. Pollak, F.A.C.P., Jersey City, N. J.—1 reprint;  
Dr. Ellen C. Potter, F.A.C.P., Trenton, N. J.—2 reprints;  
Dr. Robert M. Stecher, F.A.C.P., Cleveland, Ohio—13 reprints;  
Dr. Frederick R. Taylor, F.A.C.P., High Point, N. C.—1 reprint.

#### REGIONAL MEETING OF FLORIDA MEMBERS

A regional meeting of the Florida members of the American College of Physicians was held at Tampa, Fla., on April 29, under the chairmanship of Dr. William C. Blake, F.A.C.P., Tampa, with Dr. Kenneth Phillips, F.A.C.P., Miami, as secretary. The meeting preceded the opening of the 67th annual meeting of the Florida Medical Association.

The morning was given over to a scientific session, program for which was as follows:

"Theories of Renal Function," Dr. James A. Bradley, F.A.C.P., St. Petersburg;  
"Case Report—An Unusual Case of Tuberculosis in a Ten Year Old Girl," Dr. Douglas D. Martin, F.A.C.P., Tampa;  
"Functional Heart Disease," Dr. Norval M. Marr, F.A.C.P., St. Petersburg;  
"Death From Insulin Shock with Autopsy," Dr. H. Mason Smith, F.A.C.P., Tampa.

Members joined in the discussion of each paper. There was a luncheon meeting at noon addressed by Dr. T. Z. Cason, F.A.C.P., College Governor for Florida, Dr. Charles H. Cocke, F.A.C.P., Chairman of the Board of Governors, Asheville, N. C. and by Mr. E. R. Loveland, Executive Secretary of the College, Philadelphia. Dr. Cocke discussed the objectives of the College and the requirements for membership and Mr. Loveland discussed the activities of the College and the operation of the executive offices. Present at the meeting and the luncheon were eight guest physicians from Havana, Cuba, most of whom occupy important teaching positions in Internal Medicine or allied subjects at the University of Havana. General interest was expressed in the extension of the College membership to Cuba, with the selection of the most outstanding internists there. Present at the meeting were approximately forty of the members of the College from Florida, out of a total membership of sixty.

The regional meeting for 1941 will be held in Jacksonville. Dr. Louie Limbaugh, F.A.C.P., Jacksonville, was selected as chairman and Dr. Kenneth Phillips, F.A.C.P., Miami, was reelected secretary.

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#### RHODE ISLAND REGIONAL MEETING

On April 13 the Fellows and Associates of the American College of Physicians of Rhode Island held a regional meeting at the Rhode Island Hospital. Dr. C. F. Gormly, Physician-in-Chief of the Medical Department of the Hospital presided. The speakers were Drs. H. A. Lawson, Louis I. Kramer, Russell S. Bray, C. F. Gormly and A. M. Burgess, Fellows, and Dr. F. H. Chafee, Associate.

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Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill., spoke before the Des Moines Academy of Ophthalmology and Otolaryngology on the subject of "Allergy in Rhinology," March 25. Dr. Feinberg also held a clinic on allergy and gave a talk on the subject of "Summer Allergy" at the meeting of the Eleventh Indiana Councilor District Medical Association, on May 15, at Huntington, Ind.

The decennial meeting of the Convention for the revision of the Pharmacopoeia of the United States was held in Washington, D. C., May 14-15, 1940, under the presidency of Dr. Walter A. Bastedo, F.A.C.P., New York, N. Y.

The delegates of the American College of Physicians at this Convention were Dr. Charles F. Tenney, F.A.C.P., New York, N. Y., Dr. Torald Sollmann, F.A.C.P., Cleveland, Ohio, and Dr. Edward Dean Spalding, F.A.C.P., Detroit, Mich.

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The Seventh Annual Post-Graduate Conference of the staff of the Mercy Hospital, Wilkes-Barre, Pa., was held on April 25. Guest speakers of this meeting were: Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, Pa., who spoke on "Diabetes as a Complication of Other Diseases" and Dr. M. Herbert Barker, F.A.C.P., Chicago, Ill., who spoke on "The Ionic Control of Edema." During the evening there was a regional meeting of the Commission on Diabetes. Dr. Belford C. Blaine (Associate), Pottsville, Pa., Chairman of the Commission on Diabetes, and Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, Pa., presided. The topic of discussion was "Lay Education on Diabetes."

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The New York Cardiological Society held their regular stated meeting April 24, at the New York Academy of Medicine. Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, Pa., presented a paper on "Some of the Unsolved Problems in Electrocardiography," which was discussed by Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.

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Dr. Ralph C. Matson, F.A.C.P., Portland, Ore., has been appointed Chief Surgeon of the University State Tuberculosis Hospital in Portland.

On April 3 Dr. Matson addressed the Oregon Tuberculosis Association in Bend, Ore., on "Modern Trends in the Surgical Treatment of Pulmonary Tuberculosis." On April 5 he held a surgical clinic in the University State Tuberculosis Hospital for the Pacific Coast Surgical Society.

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Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "Diet and Nutrition in Nephritis" at the recent Fifth Annual Postgraduate Institute of the Philadelphia County Medical Society. Dr. Kelly also presented an exhibit on "Deficiency Disease" at this meeting.

On April 12 Dr. Kelly addressed the Seventh Councilor District of the Medical Society of the State of Pennsylvania in Williamsport, Pa., on "Healthful Living."

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The American College of Chest Physicians under the Presidency of Dr. Ralph C. Matson, F.A.C.P., Portland, Ore., will hold its Sixth Annual Meeting in New York, N. Y., June 8-10, 1940. Dr. George Ornstein, F.A.C.P., New York, N. Y., is General Chairman of the Scientific Program Committee; Dr. Foster Murray, F.A.C.P., Brooklyn, N. Y., is Chairman of the Medical Section; Dr. David Ulmar, F.A.C.P., New York, N. Y., is Chairman of the Surgical Section; Dr. Edward P. Eglee, F.A.C.P., New York, N. Y., is Chairman of the Clinical Section; and Dr. Edgar Mayer, F.A.C.P., New York, N. Y., is Chairman of the General Arrangements Committee. Among the features of this meeting will be two "Information Please" Luncheons. At these luncheons experts in tuberculosis will conduct round table discussions and answer various questions previously submitted. Among those who will participate in these luncheons are Dr. James Alex. Miller, F.A.C.P., New York, N. Y., Dr. Ralph C. Matson, F.A.C.P., Portland, Ore., Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill., and Dr. Carl R. Howson, F.A.C.P., Los Angeles, Calif.

Twelve other Fellows and two Associates of the College will participate in the formal program of this meeting and will present papers.

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Among those who will speak before the Section on Medicine of the Medical Society of New Jersey at their meeting in Atlantic City, June 4-6, will be the following:

Dr. Ralph K. Hollinshed, F.A.C.P., Westville, N. J.  
Dr. Thomas K. Lewis, F.A.C.P., Camden, N. J.  
Dr. Benjamin Saslow (Associate), Newark, N. J.  
Dr. Sydney R. Miller, F.A.C.P., Baltimore, Md.  
Dr. Aaron Parsonnet, F.A.C.P., Newark, N. J.  
Dr. Thomas M. Kain, F.A.C.P., Camden, N. J., is Chairman of this Section.

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The Fifth Annual Convention of the National Gastroenterological Association will be held in New York, N. Y., at the Hotel Roosevelt, June 4-6. Among those who will participate in this program are the following:

Dr. Anthony Bassler, F.A.C.P., New York, N. Y.  
Dr. Samuel Weiss, F.A.C.P., New York, N. Y.  
Dr. Clarence J. Tidmarsh, F.A.C.P., Montreal, Que., Can.  
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.  
Dr. Henry A. Rafsky, F.A.C.P., New York, N. Y.  
Dr. Hyman I. Goldstein (Associate), Camden, N. J.  
Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J.  
Dr. Manfred Kraemer, F.A.C.P., Newark, N. J.  
Dr. Burrill B. Crohn, F.A.C.P., New York, N. Y.

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Dr. Roland A. Davison, F.A.C.P., Tucson, Ariz., was one of the speakers at the annual meeting of The Arizona Hospital Association in Phoenix. The subject of Dr. Davison's address was "The Importance to Hospitals of Good Public Relations Education."

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Dr. James E. Paullin, F.A.C.P., and Dr. Cyrus W. Strickler (Associate), both of Atlanta, Ga., were among those who presented a symposium on the problems of medical care in Georgia, at the annual meeting of the Medical Association of Georgia, held at Savannah April 23-26. Dr. Kenneth M. Lynch, F.A.C.P., Charleston, S. C., gave an address on "Progress in Knowledge and Control of Cancer" at this meeting.

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Dr. Christian B. Luginbuhl, F.A.C.P., Des Moines, Iowa, has been appointed to the newly established library board of the Iowa Methodist Hospital. Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa, recently donated 225 volumes to this library.

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Dr. Elston L. Belknap, F.A.C.P., Milwaukee, Wis., was one of the speakers who addressed the annual meeting of the Michigan Association of Industrial Physicians and Surgeons on April 17 in Grand Rapids, Mich. The subject of Dr. Belknap's address was "Silicosis—Wisconsin Plan."

Among those who addressed the recent annual meeting of the Missouri-Kansas Neuropsychiatric Association in Kansas City, Mo., were:

Dr. Walter Freeman, F.A.C.P., Washington, D.C.—“The Wincing Reaction”;  
Dr. George T. Harding, F.A.C.P., Columbus, Ohio—“The Treatment of Psychiatric Patients in the Private Hospital.”

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Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., addressed the Kansas City Academy of Medicine, April 19, on “Chemotherapy in Respiratory Diseases.”

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Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, Md., addressed a meeting of the Broome County Medical Society at Binghamton, N. Y., March 12, on “Hypertension, Its Clinical Significance and Treatment.”

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Dr. Lay Martin, F.A.C.P., Baltimore, Md., was one of those who addressed the New York chapter of the National Gastroenterological Association March 18. The subject of his address was “Prolonged Partial Obstruction of the Small Intestine.”

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Dr. Mark A. Griffin, F.A.C.P., Asheville, N. C., was elected President of the North Carolina Neuropsychiatric Society at their recent meeting in Charlotte, N. C.

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President-elect Roger I. Lee, F.A.C.P., Boston, Mass., addressed the Columbia Medical Society (S. C.), March 11, on hypertension.

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Dr. George R. Wilkinson (Associate), Greenville, S. C., was one of those elected vice president of the Tri-State Medical Association of the Carolinas and Virginia at the annual meeting in Richmond, February 26-27.

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On April 25, Dr. Burt R. Shurly, F.A.C.P., Detroit, Mich., was presented with a gold medal, which had been awarded him by the American Academy of Ophthalmology and Otolaryngology at its 1939 annual session for noteworthy contributions to the knowledge of nose and throat disorders. Presentation of this medal was made at a testimonial dinner in Detroit in honor of Dr. Shurly.

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Among those who spoke at the annual meeting of the Society for the Study of Asthma and Allied Conditions in Atlantic City, N. J., April 29, were:

Dr. Robert A. Cooke, F.A.C.P., New York, N. Y.—“Sensitizations Induced by Tetanus Toxoid”;  
Dr. George Piness, F.A.C.P., Los Angeles, Calif.—“Relationships Between Foods as Shown by the Skin Test in 1,000 Children”;  
Dr. Louis E. Prickman, F.A.C.P., and Dr. Herman J. Moersch, F.A.C.P., both of Rochester, Minn.—“The Diagnosis and Treatment of Bronchostenosis, an Important Complication of Asthma.”

Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa, was reelected secretary of the Federation of State Medical Boards of the United States at their recent meeting in Chicago, Ill.

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Dr. Samuel R. Haythorn, F.A.C.P., Pittsburgh, Pa., was elected vice president and Dr. Howard T. Karsner, F.A.C.P., Cleveland, Ohio, was elected secretary of the American Association of Pathologists and Bacteriologists at their annual meeting in Pittsburgh, Pa., on March 21.

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The Walter Jarvis Barlow Society of the History of Medicine recently created a lectureship in honor of Dr. George Dock, F.A.C.P., Pasadena, Calif. Dr. Dock presented the first lecture at a dinner in his honor. The subject of his address was "A Dictionary of Medical Biography."

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The following Fellows of the College spoke at the sixty-first annual meeting of the Louisiana State Medical Society held in New Orleans, April 22-24:

- Dr. Byrl R. Kirklin, Rochester, Minn.—"Solving Problems in the Diagnosis of Diseases of the Lungs";  
Dr. John H. Musser, New Orleans, La.—"Typhus Fever in Louisiana";  
Dr. Daniel N. Silverman, New Orleans, La.—"Early Diagnosis and Treatment of Amebic Abscess of the Liver."
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At the eighty-third annual session of the Missouri State Medical Association held in Joplin, Mo., April 29-May 1, the following Fellows of the College participated:

- Dr. Cyrus C. Sturgis, Ann Arbor, Mich.—"Prognosis and Treatment of Hypertension";  
Dr. John H. Musser, New Orleans, La.—"Treatment of Some of the Contagious Diseases";  
Dr. Nathan B. Van Etten, New York, N. Y.—"An American Health Program."
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Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, delivered the tenth course of lectures under the Porter Lectureship in Medicine of the University of Kansas. On April 30 he lectured on "Hemolytic Anemia" and on May 1, on "The Red Blood Cell of Man" and "Polycythemia."

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Dr. George R. Herrmann, F.A.C.P., Galveston, Texas, was the speaker at a joint meeting of the St. Louis Medical Society and the St. Louis Clinics, during the annual postgraduate course and clinical conference of the St. Louis Clinics, held in St. Louis, Mo., May 14. The subject of Dr. Herrmann's address was "Recognition and Management of the Common Circulatory Emergencies."

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At the annual meeting of the Medical Society of the State of New York, held in New York City, May 6-9, Capt. Harry G. Armstrong, (MC), U.S.A. (Associate), spoke on "General Medical Problems in Aviation" and Lieut. Col. William D. Fleming, (MC), U.S.A., F.A.C.P., spoke on "Medical Problems in Aviation."



On April 4 Dr. Paul Dudley White, F.A.C.P., Boston, Mass., delivered the fifteenth Hermann Michael Biggs Memorial Lecture of the New York Academy of Medicine. The subject of Dr. White's lecture was "Heart Disease—A World Problem."

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On May 1 Dr. Thomas Addis, F.A.C.P., San Francisco, Calif., delivered the Adam M. Miller Memorial Lecture at the Long Island College of Medicine, Brooklyn, N. Y. The subject of his address was "The Anatomical and Physiological Concepts Underlying the Treatment of Glomerular Nephritis."

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Dr. Oscar W. Bethea, F.A.C.P., New Orleans, La., was one of the guest speakers at the ninety-second annual meeting of the South Carolina Medical Association in Charleston, April 30–May 2.

At this meeting Dr. Robert Wilson, F.A.C.P., Dean of the Medical College of the State of South Carolina, was presented with the distinguished service plaque by the American Legion.

## OBITUARIES

## ALFRED JAMES SCOTT

Dr. Alfred James Scott, F.A.C.P., of Los Angeles died at his home on the seventeenth of April of coronary disease. From the first attack four years ago he had led a restricted existence. Dr. Scott was born in Michigan, September 28, 1881. He came to Los Angeles as a young man and was a telegraph operator prior to and while he was studying medicine at the Southern Branch of the University of California from which he was graduated in 1909. He entered private practice, soon limiting his work to pediatrics and becoming a Clinical Instructor at the Southern Branch of the University of California. He taught pediatrics at the Medical Department of the University of Southern California from 1912 to 1920 and was a Clinical Professor in the same subject in the College of Medical Evangelists from 1920 until 1934. He was a member of the Staff of the Los Angeles General Hospital and of the California Hospital. He was an examiner for the selective service Draft Board 1918-1919 and was president of the California Babies Hospital 1920 to 1931. He was a fellow of the American Academy of Pediatrics and a founder of the South Western Pediatric Society.

Dr. Scott was a member of many public spirited movements; he was a member of Alpha Kappa Kappa Fraternity, the University Club and was a Mason and Shriner. He belonged to numerous medical and civic organizations which are more fully listed in "Who's Who." His widow, son and daughter, in addition to his brothers and sisters and a wide medical acquaintance feel the loss of a fine man and citizen and a good physician.

EGERTON L. CRISPIN, M.D., F.A.C.P.,

Regent

## SIDNEY DEAN WILGUS

Dr. Sidney Dean Wilgus, F.A.C.P., died on February 23, at his home in Rockford, Ill., at the age of sixty-eight, of coronary occlusion.

Dr. Wilgus was born in Buffalo, N. Y., February 16, 1872, and received his early education in the public schools of that city. In 1895 he received the degree of Doctor of Medicine from the University of Buffalo. From 1895 until 1902, he was Assistant Physician at St. Lawrence (N. Y.) State Hospital; he then served the next two years as Psychiatrist of Kings County and Bellevue Hospitals in New York, N. Y. In 1904 Dr. Wilgus was appointed Chairman of the New York State Board of Alienists. He served in this capacity until 1910, when he moved to Illinois to become managing officer of the Elgin State Hospital. Between 1911 and 1913 he served as managing officer of the Kankakee State Hospital. In 1913 Dr. Wilgus founded the Wilgus Sanitarium near Rockford, Ill. He was Medical Di-

rector of this institution until his death. He served as Staff Member and Lecturer in Psychiatry at the Rockford Hospital for many years, as Illinois State Alienist from August, 1929, until July, 1933, and as Professor of Psychiatry and Head of the Department of Psychiatry at Chicago Medical College since 1936.

Dr. Wilgus saw active service in both the Spanish-American War and in the World War. During the World War he served as a member of the Medical Appeal Board and performed a special hospital inspection service for the Office of the Surgeon General. In 1922 he was appointed a Major in the Medical Officers' Reserve Corps, United States Army, and in 1930 became a Lieutenant Colonel. During 1925 and 1926 he served as President of the Reserve Officers' Association of Illinois.

Dr. Wilgus was always deeply interested in the study of psychiatry. During 1927 he undertook postgraduate study in this field in Vienna. He took an active part in several psychiatric research projects of the National Committee for Mental Hygiene. One of the most important of these was a survey of conditions surrounding the care of the insane and feeble-minded in four states.

Dr. Wilgus was a member of the American Psychiatric Association, the Central Neuropsychiatric Association, the Chicago Neurological Society, of which he was President during 1932, a Fellow of the American Medical Association, and a Fellow of the American College of Physicians since 1930.

The death of Dr. Wilgus ends a distinguished career of one of the pioneers of psychiatry.


### WILLIAM GEORGE FALCONER

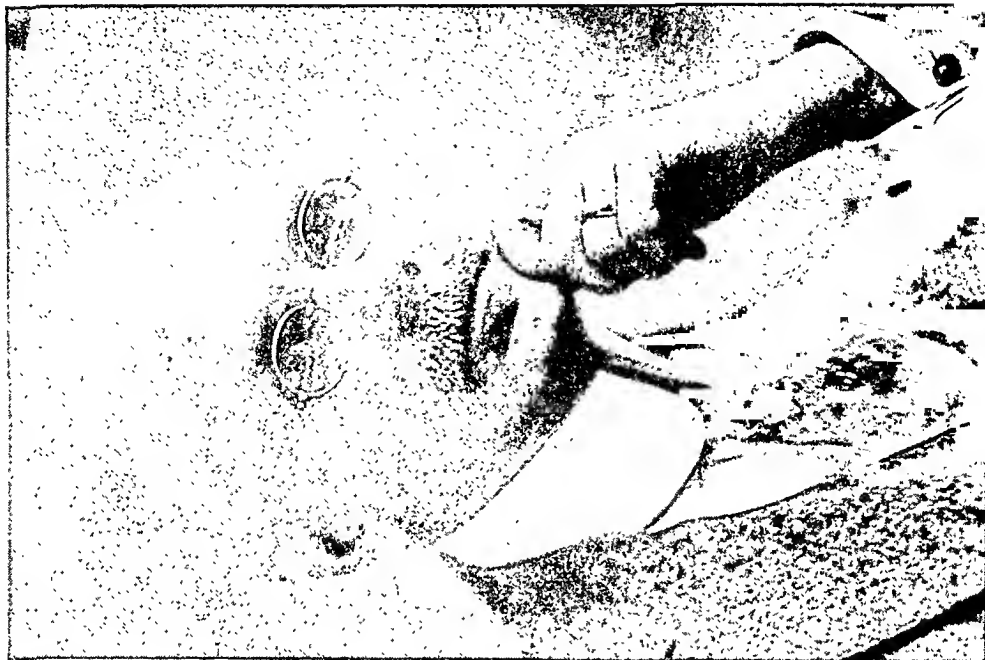
Dr. William George Falconer, F.A.C.P., Clearfield, Pa., died January 3, 1940, of coronary occlusion. Dr. Falconer was born at Woodland, Pa., September 22, 1888. He attended the Perkiomen School and Pennsylvania College at Gettysburg. His medical training was received at Jefferson Medical College, from which institution he was graduated in 1919. He pursued postgraduate work at Harvard University and for many years was a member of the Medical Service and Chief of the Heart Clinic of the Clearfield Hospital. Dr. Falconer was a member of the Clearfield County Medical Society, Pennsylvania State Medical Society and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1926.

### SAMUEL OSBORN

Dr. Samuel Osborn, F.A.C.P., Lansing, Mich., died December 4, 1939, at the Edward W. Sparrow Hospital of coronary thrombosis following a prostatic resection. Dr. Osborn was born at Manchester, Mich., in 1866;

received his degree of Bachelor of Science in Chemistry from the University of Michigan and his medical degree from the University of Michigan Medical School in 1903. He interned at the University of Michigan Hospital, 1903-04, and served an additional year as House Physician. Thereafter he became House Physician to the Chicago Lying-In Hospital and Dispensary, 1905. He pursued postgraduate work on two different occasions at the Massachusetts General Hospital, Boston, and also at the University of Michigan Hospital. In recent years he had retired from hospital work. He was a past president of the Ingham County Medical Society, a member of the Michigan State Medical Society and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1923.





WILLIAM GERRY MORGAN  
MASTER OF THE AMERICAN COLLEGE OF PHYSICIANS



JAMES B. HERRICK  
MASTER OF THE AMERICAN COLLEGE OF PHYSICIANS

## PROCEEDINGS OF THE TWENTY-FOURTH ANNUAL SESSION (CONTINUED)

### THE ELECTION OF MASTERS

For the first time in eleven years the Board of Regents added to the rôle of Masters of the College by awarding this title to two eminent Fellows who have rendered distinguished service to the College:

- Dr. James B. Herrick, Emeritus Professor of Medicine of Rush Medical College, holder of the Distinguished Service Medal of the American Medical Association, Ex-Regent and Ex-Vice President of the American College of Physicians.
- Dr. William Gerry Morgan, Emeritus Dean and Professor of Gastro-enterology of Georgetown University School of Medicine, Regent of Georgetown University, Ex-President of the American Medical Association, Ex-Vice President, Ex-Secretary General, Ex-Governor, Ex-Regent and now Historian of the American College of Physicians.

### THE ANNUAL BUSINESS MEETING

The Annual Business Meeting of the College was opened by President O. H. Perry Pepper, with the following address:

PRESIDENT O. H. PERRY PEPPER: "It is Carlyle who is always quoted as saying: 'Happy the people whose annals are blank in history books,' but he copied it from Montesquieu who probably got it from some one else. So there is no theft in my saying 'Happy is the retiring officer whose term has seen no history made.' Certainly it seems to me that the past year has seen nothing but steady healthy growth in our College. Growth in membership which now equals 4,456; growth in financial security of which you will hear from the Treasurer; growth in College usefulness with, for the first time, five research fellowships awarded; a bigger and better journal still happily under the excellent editorship of Doctor Pincoffs; with increased participation in graduate education as evidenced by successful pre-meeting courses, local gatherings of our Fellows and friendly but unentangled coöperation with other agencies toward a study of this entire problem.

"Our offspring, the American Board of Internal Medicine, is growing up a credit to both its parents, and as you heard from Doctor Irons on Monday, is now well established, financially independent and already exerting a strong and healthy influence on medicine on this continent. Our College continues to name a majority of the members of that Board, whose certification now becomes obligatory for promotion to Fellowship of Associates elected after this meeting. This is an important step which will go down in our history books and was not taken without grave debate by the Regents. I am proud that this step was made during my year as President.

"Our College Headquarters continue to prove ideal for their purposes and the cost of maintenance has been even less than our most sanguine expectations. Our Headquarters staff continues efficiently to make life easy for the President not only by telling him what he should do but by then doing all the hard work for him. Mr. Loveland scared this President out of his wits by having to undergo a serious surgical operation. I never was more interested in the recovery of anybody and I congratulate the College on the complete recovery of their Executive Secretary.

"One thing that transforms the President's task into an easy one is the wholehearted coöperation which he received from Regents and Governors. A Committee once appointed, the President knows the work will be done. I seriously doubt if the membership of the College has any idea of the amount of hard, time-consuming, self-sacrificing committee work that is done by the Governors and Regents of the College. There is a unanimity of willingness to serve which would dismay any pessimist who thinks that man is motivated only by selfishness, jealousy and laziness.



JAMES D. BRUCE  
PRESIDENT (1940-41), ANN ARBOR, MICH.



O. H. PERRY PEPPER  
RETIRING PRESIDENT, PHILADELPHIA, PA.

"Another thing that helps the President is the assistance he gets on all hands in the making up of the program. First in the matter of the General Chairman and local committees; this also is hard work and means sacrifice. No one refuses, every one jumps at the chance to serve. The same spirit is shown with regard to the program of the General Sessions and the Lectures. This year I wanted to emphasize our own membership in both these groups and I had fine help. It is my belief that a place on our program should be a prize to be striven for by our younger members and that it should be granted within reason in order to stimulate good work and to give training in the preparation and presentation of papers.

"Onward the College goes and it is a tremendous thing for an individual to have been permitted to march along with all the others who are doing their bit to advance the American College of Physicians."

Dr. William D. Stroud, Treasurer, presented the following report:

"The accounts of the College for 1939, have been audited by a Certified Public Accountant and scrutinized by the Committee on Finance. The year's operations indicate continued growth and a satisfactory financial situation. Through growth in Life Membership subscriptions and a transfer of approximately \$30,000.00 in securities by the Board of Regents from the General Fund, the Endowment Fund on December 31, 1939, amounted to \$97,499.76. The General Fund totalled \$148,453.43, making the total College assets, at book value, \$245,953.19. The net increase in capital, for both funds, was \$23,939.07. In spite of increased activities, an appropriate credit balance was maintained. One of the former Pittsburgh depositories of the College which failed has now liquidated in full the original amount to the College, and the other two closed banks have materially reduced the balances still owing. Copies of the financial reports for 1939 will be published in an early issue of the 'Annals of Internal Medicine' for the information of all members.

"On the recommendation of the Finance Committee and the subsequent approval of the Board of Regents, the budget for 1940 has been adopted, calling for an estimated income of \$105,600.00 and estimated expenditures of \$80,875.00."

Mr. E. R. Loveland, Executive Secretary, presented his annual report covering all features of progress and activities in the College, dealing with membership, the publication of the Directory, handling the postgraduate courses, administering the College Headquarters, publication of financial operations, promotion of the circulation of the ANNALS OF INTERNAL MEDICINE and the general administration of the Annual Session in Cleveland.

Dr. George Morris Piersol, Secretary General, presented the following report:

"Since the last Annual Session of the College, the membership report shows that three Fellows and one Associate have been dropped for delinquency; the resignations of three Fellows and two Associates have been accepted; One Master, thirty-two Fellows and eleven Associates have been lost by death. Twenty-three Associates were dropped for failure to qualify for Fellowship within the maximum five-year period, as prescribed by the By-Laws. This year two Fellows were elected to Mastership; two hundred fifty-eight were elected to Fellowship, the majority of whom were advancements from Associateship. Only seventeen were elected directly to Fellowship because of their special qualifications and outstanding accomplishments. Two hundred ninety-two have been elected to Associateship.

"The total membership of the College is now constituted as follows:

Masters .....	3
Fellows .....	3,188
Associates .....	1,265
Total .....	<u>4,456</u>



“Eighteen Fellows have become Life Members since the last Annual Meeting, making a total of one hundred thirty-four names now on the Life Membership Scroll. Of the Life Members, twelve are deceased, leaving one hundred twenty-two.

“Attention should be called to the resolution of the Board of Regents passed at their regular meeting on December 17, 1939, modifying the qualifications for Fellowship. The resolution is as follows:

‘RESOLVED, that after April 6, 1940, all candidates for Fellowship must present satisfactory evidence of certification by their national board for certification in their particular field, where such a board exists; this rule shall not apply to candidates from the Army, Navy and Public Health Services; it shall not apply to those who have been elected Associates prior to the above date; it may be waived in the cases of those proposed directly for Fellowship because of exceptional and outstanding qualifications.’

“In other words, regardless of their other qualifications, no Associate hereafter elected may be advanced to Fellowship who has not been certified by his or her national board of certification where such exists, except under unusual circumstances as set forth in the regulations laid down by the Board of Regents.

“It should be emphasized that the above mentioned resolution is not retroactive, and, therefore, does not apply to those who are now Associates.

“Thanks to the untiring efforts of the Committee on Postgraduate Education and the wholehearted coöperation of the Board of Governors and many of our Fellows, the intensive postgraduate courses that have preceded this Annual Session have increased in number, interest and scope. Admission to these courses has been restricted, as formerly, to members of the College and those attempting to qualify for Associateship or advancement to Fellowship. This year five were given:

- Course No. 1, “General Medicine,” Ann Arbor
- Course No. 2, “Medicine in Industry,” Detroit
- Course No. 3, “Allergy,” New York
- Course No. 4, “Hematology,” Columbus
- Course No. 5, “Cardiovascular Diseases,” Iowa City

“The total registration for these courses numbers 144, in spite of the fact that the registration for each course was more limited than formerly. Every course was filled, and for some courses there was a considerable waiting list. This postgraduate teaching has become one of the most important activities of the College. It is steadily gaining in popularity and justifies further development.

“Five Research Fellowships have been awarded by the College this year. These Fellowships go into effect July 1 next. They constitute another important and constructive educational activity of this organization.”

At the end of his report, Dr. Piersol turned to the retiring President.

“Mr. President, in the past year, during which you have so ably and wisely guided the destiny of this College, you have become more than ever endeared to all who have had the privilege of working with you. We are deeply appreciative of the never-failing spirit of coöperation and courtesy that has marked all our associations.

“Therefore, on behalf of the Officers, Regents and Governors of the American College of Physicians, I have the honor to present you with this Gavel, an enduring symbol of the high office which you have held, as well as a token of our affection and esteem.”

(Dr. Piersol presented the gavel to Dr. Pepper.)

DR. PEPPER: “Even pleasant memories tend to fade in our minds and I accept this gavel with deep satisfaction as a permanent reminder of the pleasure that I have experienced from my associations with the Regents, Governors and members of the College during my year as President.”

At this point, Dr. James D. Bruce, President-Elect, was inducted as President of the College for 1940-41.

PRESIDENT BRUCE:

"MEMBERS OF THE COLLEGE: The most outstanding tendency of medicine of this generation in America is the place and opportunity given to the younger men. As a result of this, certain observable tendencies have developed of which this College and other special societies are important evidences.

"From time to time there is questioning of the requisites and standards of the various qualifying boards. In the progress of American medicine, the organization of the various special societies and the establishment of the qualifying boards rank in importance with the reorganization of the undergraduate schools about the turn of the century. In the latter, meeting the new standards entailed added burdens upon even the most favorably situated schools and a real hardship upon many, while more than half the proprietary schools were compelled to close their doors—all this quite apart from the additional hurdles for the undergraduate student. The establishment of the qualifying boards has raised new problems, comparable, at least in part, to those of a generation ago, and the means whereby the candidate may be enabled to meet the requirements now constitute a real problem for this and other similar organizations.

"The College of Physicians has assumed certain obligations which include the establishment of programs of education designed to keep our members at desirable levels of proficiency, the organization of resources to permit worthy candidates to prepare themselves for the Board of Internal Medicine and membership in the College, and the encouragement and support of research. The effective integration of all these functions justifies our use of the term *college*.

"Probably one of the reasons why misunderstanding of objectives sometimes arises is that while we may all speak fairly good English, we may not speak the same educational and professional language. In Dr. Pepper's classical dissertation on the term *internist*, he had recourse to the dictionary and while definitions therein are sometimes confusing we do get a great deal of light on the origin and meaning of words. Following Dr. Pepper's suggestion, let us turn to the dictionary to learn what it has to say about the word *college*. Here it is in part: 'pertaining to or in the nature of a college or a body of colleagues.' 'Colleague' comes from the same root as 'college.' A college then means literally 'a company or partnership of colleagues.' It may describe 'a body of persons engaged in common pursuits or having common duties and interests and sometimes, by charter, peculiar rights and privileges,' or 'a company of scholars or friends of learning incorporated for study and instruction in the higher branches of knowledge, usually of a professional kind.' The main point is that a college is an institution or organization where there is a body of self-governing associates or equals bound together in the pursuit of their common interests and having certain powers and privileges conferred on them or delegated to them.

"It would seem then with the establishment of the Board of Internal Medicine, a qualifying agency, that the College with programs such as these in which the various phases of medical advances are reviewed and brought up to date, with a program of postgraduate education so well received by our members and those desirous of membership, together with the encouragement and support given to scientific research, is filling the function of and entitled to the honored designation of *college*.

"As I review the qualifications required by the Board of Internal Medicine and the College, it leaves me with but one major concern, and that is the seeming impossibility of the attainment of college affiliation by a not inconsiderable group of younger internists; not, indeed, through the stringency of the requirements of the Board but through the fact that we have in this country at the present time too limited opportunities to provide requisite disciplines and experiences for prospective candidates for membership. Thus I was particularly pleased with the commission from Dr. Pepper to attend a meeting with Dr. Hugh J. Morgan, chairman of our Postgraduate Committee; Dr. Ernest E. Irons, chairman of the Board of Internal

Medicine, and Dr. W. D. Cutter, secretary of the Council of the American Medical Association, for a discussion of the mutual interests and responsibilities of the educational and qualifying phases of these collaborating agencies. Here I was gratified to find complete awareness of the urgent importance of the problems and a determination to give a maximum flexibility to the requirements of the Board, without any thought of a lowering of standards.

"Were I to select that which in my opinion is the most important task for the College during the coming year, it would be the assembling and utilizing of all our present educational resources and adding, as rapidly as may safely be done, new methods whereby candidates may qualify, having in mind at all times the objectives of the College and the standards set up by the Board.

"I would take the system we know, suggesting how it might be strengthened where it is weak, repaired where it has crumbled, and rebuilt where new needs require additions to its fabric. . . . While social, economic and other humanistic factors are a part of the fabric, the basic thought in all these considerations must be toward the advancement of science and its utilization for human needs. No body of medical men has this goal more clearly in mind than the American College of Physicians.

"I am not unmindful of the great honor you have conferred upon me. For this I thank you. Also, I am not unmindful of the responsibilities of this high office. May I express the hope that any lack in professional preparedness or administrative ability will be, at least in part, compensated for by the devotion and humility with which I approach the task."

President Bruce called upon Dr. Sydney R. Miller, Chairman of the Committee on Nominations, to present the nominations for the elective offices, for the Board of Regents and for the Board of Governors, according to the terms of expiration for the current year.

DR. SYDNEY R. MILLER: "Mr. President, the Nominating Committee, composed of Dr. William J. Kerr, Dr. James J. Waring, Dr. Charles E. Watts, Dr. Clarence L. Andrews, and myself, nominate the following for office:

*"(A) For the Elective Offices:*

*President-Elect* ..... Roger I. Lee, Boston, Mass.  
*First Vice President* ..... Robert A. Cooke, New York, N. Y.  
*Second Vice President* ..... James G. Carr, Chicago, Ill.  
*Third Vice President* ..... Henry M. Thomas, Jr., Baltimore, Md.

This list of nominees has been duly published in the 'ANNALS OF INTERNAL MEDICINE' at least one month before the present date."

There were no nominations from the floor and on motion, seconded and duly carried, nominations were closed and the Secretary General was instructed to cast the ballot for the above nominees.

DR. MILLER:

*"(B) For the Board of Regents:*

*Term Expiring 1941*

T. Homer Coffen, Portland, Oregon

*Term Expiring 1943*

David P. Barr, St. Louis, Mo.  
 J. Morrison Hutcheson, Richmond, Va.  
 Walter W. Palmer, New York, N. Y.  
 O. H. Perry Pepper, Philadelphia, Pa.  
 Gerald B. Webb, Colorado Springs, Colo."

There were no nominations from the floor and on motion duly seconded and carried, nominations were closed and the Secretary General was instructed to cast the ballot for the election of the above nominees to the Board of Regents.

DR. MILLER:

" (C) *For the Board of Governors:*

*Term Expiring 1943*

Fred W. Wilkerson, Montgomery	.....ALABAMA
Fred G. Holmes, Phoenix	.....ARIZONA
Lewis B. Flinn, Wilmington	.....DELAWARE
Turner Z. Cason, Jacksonville	.....FLORIDA
Glenville Giddings, Atlanta	.....GEORGIA
LeRoy H. Sloan, Chicago	.....ILLINOIS (Northern)
C. W. Dowden, Louisville	.....KENTUCKY
Eugene H. Drake, Portland	.....MAINE
Louis Krause, Baltimore	.....MARYLAND
John G. Archer, Greenville	.....MISSISSIPPI
Ernest D. Hitchcock, Great Falls	.....MONTANA
LeRoy S. Peters, Albuquerque	.....NEW MEXICO
Charles F. Tenney, New York	.....NEW YORK (Eastern)
A. B. Brower, Dayton	.....OHIO
Homer P. Rush, Portland	.....OREGON
M. D. Levy, Houston	.....TEXAS
Elmer L. Sevringhaus, Madison	.....WISCONSIN
Ramon M. Suarez, San Juan	.....PUERTO RICO
George F. Strong, Vancouver	.....ALBERTA, BRITISH COLUMBIA, MANITOBA, SASKATCHEWAN "

There were no nominations from the floor and on motion duly seconded and carried, nominations were closed and the Secretary General was instructed to cast the ballot for the election of the above Governors.

President Bruce requested Dr. D. Sclater Lewis and Dr. John H. Musser to escort the new President-Elect, Dr. Roger I. Lee, to the rostrum.

President Bruce introduced Dr. Lee amid wide applause.

The following resolution, moved by Dr. Charles F. Tenney and seconded by Dr. Hugh Morgan, and unanimously carried, was spread upon the Minutes:

"RESOLVED, that the cordial thanks of the American College of Physicians be extended to the Retiring President, Dr. O. H. Perry Pepper; to the General Chairman, Dr. Howard T. Karsner; to the chairman and members of his various committees, individually and collectively, to the Cleveland Academy of Medicine, for their faithful work in the preparation and conduct of the Cleveland Session; to the Ladies Entertainment Committee for its efficiency, hospitality and courteous entertainment of our ladies; to the Western Reserve University and the hospitals and institutions of Cleveland for putting their facilities at the disposal of the College, and for their helpful participation; to the public press; to the Cleveland Convention and Visitors' Bureau and its officers for their assistance; to the Cleveland Public Auditorium and its staff for coöperation and help; to the Hotel Statler for its assistance and aid in providing for our entertainment and comfort."



## GENERAL FUND

For the Year Ended December 31, 1939

Balance, January 1, 1939.....		\$153,449.87
Less:		
Transfer to Endowment Fund of the Initiation Fees of Life Members	\$ 970.00	
Transfer to Endowment Fund per resolution of Board of Regents, December 17, 1939.....	29,811.03	30,781.03
		<u>\$122,668.84</u>

## Summary of Operations for the Year ended December 31, 1939:

## Income:

Annual Dues.....	\$27,597.89
Initiation Fees.....	15,506.00
Subscriptions, ANNALS OF INTERNAL MEDICINE....	29,930.31
Advertising, ANNALS OF INTERNAL MEDICINE.....	9,198.90
Income from Invested Funds, General.....	4,683.49
Income from Invested Funds, Endowment.....	2,674.33
Exhibits, 23rd Annual Session.....	11,671.44
Guest Fees, 23rd Annual Session.....	530.00
Banquet, net, 23rd Annual Session.....	298.61
Profit on Keys, Pledges and Frames.....	196.45
Dividend on Perpetual Insurance Deposit.....	60.00
Profit on Equipment Sold.....	7.50
Sale of Directory, 1937.....	4.95
Total Income.....	<u>\$102,359.87</u>

## Expenses:

Salaries.....	\$23,843.45
Postage, Telephone and Telegraph.....	3,763.12
Office Supplies and Stationery.....	1,199.15
Printing.....	22,257.42
Traveling Expenses.....	6,390.22
College Headquarters:	
Maintenance.....	\$1,581.38
Heat, Light, Gas and Water.....	612.90
Taxes.....	1,176.22
Insurance.....	82.16
Loss on Sale of Investments, General Fund.....	3,452.66
Depreciation on Building, Furniture and Equip- ment.....	1,200.71
Grant to Commission on Graduate Medical Educa- tion.....	1,758.96
1939 Directory, net.....	100.00
Postgraduate Courses, net.....	2,524.84
John Phillips Memorial Prize.....	481.43
Research Fellowships.....	41.75
Other Expenses:	
23rd Annual Session.....	2,713.50
ANNALS OF INTERNAL MEDICINE....	\$4,813.55
Miscellaneous.....	470.46
	<u>1,564.06</u>
Total Expenses.....	6,848.07
Net Income for the Year Ended December 31, 1939.....	\$76,575.28
Balance, December 31, 1939.....	<u>\$ 25,784.59</u>
	<u>\$148,453.43</u>

## ENDOWMENT FUND

For the Year Ended December 31, 1939

Principal Account, January 1, 1939.....		\$ 68,564.25
Add:		
Life Membership Fees received during 1939.....	\$ 2,350.00	
Transfer of Initiation Fees of New Life Members from General Fund.....	970.00	
Transfer from General Fund, per resolution of Board of Regents, December 17, 1939.....	29,811.03	33,131.03
		<u>\$101,695.28</u>

Deduct:		
Loss on Sale of Investments.....	4,195.52	
Principal Account, December 31, 1939.....	\$ 97,499.76	
Income Account:		
Income from Investments earned during 1939.....	\$ 2,674.33	
Deduct:		
Research Fellowships.....	\$ 2,713.50	
John Phillips Memorial Prize.....	41.75	2,755.25
Excess of Expenses over Income, charged to General Fund Operations for 1939	\$ 80.92	

INVESTMENTS  
December 31, 1939

Par Value	Bonds	Endowment Fund Investments	General Fund Investments
\$ 3,000	Appalachian Electric Power Co., Deb., 4½s, 1948	\$ 3,105.00	
5,000	Carolina Clinchfield & Ohio Ry., 1st & Consol. Mort., Series "A," 6s, 1952.....	5,413.40	
5,000	Florida Power Corp., 1st Mort., Series "C," 4s, 1966.....	4,485.90	
5,000	Great Northern Ry., Gen. Mort., Series "B," 5½s, 1952.....	4,463.45	
5,000	Michigan Consolidated Gas, 1st Mort., 4s, 1963..	5,130.95	
5,000	North American Co., Deb., 3½s, 1949.....	5,219.52	
5,000	Northern States Power Co., 1st & Ref. Mort., 3½s, 1967.....	4,806.25	
5,000	Ohio Edison Co., 1st Mort., 4s, 1965.....	5,287.50	
4,000	Ohio Public Service, 1st Mort., 4s, 1962.....	4,240.75	
5,000	Pennsylvania RR, Gen., 4¼s, Series "E," 1984..	5,013.10	
2,000	Port of New York Authority, Interstate Tunnel, Series "E," 4¼s, 1958.....	2,065.40	
2,000	U. S. Treasury, 4s, 1944/54.....	1,998.13	
20,000	U. S. Treasury, 3¼s, 1945.....	19,887.50	
5,000	Virginia Public Service, 1st & Ref., 5½s, 1946..	5,133.65	
<u>\$76,000</u>	TOTAL, Bonds.....	<u>\$76,250.50</u>	
Shares	Stocks		
50	American Brake Shoe & Foundry Co., Conv., Pfd.	\$ 6,163.60	
50	American Gas & Electric Co., \$6.00, Pfd.....	5,537.25	
50	Atchison, Topeka & Santa Fe, 5%, Pfd.....	4,970.75	
20	Central New York Power Corp., 5s, Pfd.....	1,944.45	
100	Chase National Bank of New York.....	4,550.00	
100	Commercial Investment Trust Corp., Common..	5,143.25	
50	Continental Can Co., \$4.50, Cum. Pfd.....	5,125.00	
100	Curtiss-Wright Corp., Class A.....	2,652.80	
50	E. I. du Pont, 6%, Cum., Deb.....	6,899.00	
25	Eastman Kodak Co., Common.....	4,200.38	
75	General Motors Corp., Common.....	3,594.53	
40	Great Atlantic & Pacific Tea Co., 7%, 1st, Pfd..	5,133.75	
20	Gulf States Utilities, \$6.00, Cum. Pfd.....	2,245.30	
50	International Harvester, 7%, Pfd.....	8,169.00	
50	International Nickel Co. of Canada, Ltd., Common.....	2,432.10	
20	J. C. Penney Co.....	1,375.30	
50	Johns-Manville Corp., Pfd.....	6,326.10	
40	Monsanto Chemical Co., \$4.50, Cum. Pfd., A...	4,715.30	
50	Montgomery Ward & Co., Inc., Common.....	2,594.75	
150	Pacific Gas & Electric Co., 6%, Pfd.....	4,640.50	
50	Timken Roller Bearing Co.....	3,407.25	
	TOTAL, Stocks.....	<u>\$13,294.00</u>	<u>\$78,526.36</u>
	TOTAL, Investments.....	<u>\$89,544.50</u>	<u>\$168,070.86</u>

# ANNALS OF INTERNAL MEDICINE

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## MEDICAL PROBLEMS ENCOUNTERED IN MILITARY SERVICE \*

By CHARLES C. HILLMAN, B.S., M.D., F.A.C.P., Colonel,  
Medical Corps, U. S. Army

IN the world about us we now witness millions of people arrayed in bitter conflict against other millions, defenseless masses dying at the hands of ruthless aggressors, and commerce of neutrals as well as belligerents disrupted. We see peaceful peoples crushed by the humiliating demands of powerful neighbors and their cities leveled by the lightning thrusts of mechanized armies. We are confronted with unexpected and powerful coalitions, which are prompted solely on principles of expediency and greed. With these developments in current history we cannot but ponder over the future that fate holds in store for the American people and respond to the impulse for preparation against the possibility of an evil day that may befall us.

In contemplation of the duties which the Medical Department must assume as a component of the military forces of the United States, it has been deemed appropriate to review at this time some of the problems that are more professional in character which we as medical officers shall face in the event of war. To emphasize the fact that these are not purely academic considerations but are, on the contrary, very practical matters with which many of you may be intimately concerned, permit me to remind you that in case of a major mobilization it is estimated that we shall require from 15,000 to 40,000 commissioned officers in the Medical Department alone.

During the first phase of the conflict we shall be concerned with the mustering of manpower and the collection of thousands of young men from diverse localities into reception centers for equipment and training. The first effort of the newly mobilized medical officer will be directed to the physical examination of recruits and of registrants under the selective service act. No doubt all of you have considered the theoretical advantage of sending all the morons and the psychopaths promptly to the front, but un-

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\* Read at the Cleveland Meeting of the American College of Physicians, April 1, 1940.



fortunately a superior army cannot be moulded from inferior individuals. The first call will be for the best of our young manhood, for individuals who can withstand the mental as well as the physical strains of war, and for men who have the intelligence to perform any of the multitudinous and hazardous tasks that may fall to the soldier in the field and during combat. Besides selecting men who may be expected to perform the most rigorous duties under conditions of adversity, the military surgeon has the equally important duty of excluding those of substandard mentality and physique. A weakling at the front is worse than useless; besides being of no value himself he will often require the time of an able soldier to give him care. Moreover, he quickly gravitates into the ranks of the compensable and comes out of the war with only a pension to his credit.

Since it is important for the individual as well as for his associates and for the pension rolls to exclude cases of pulmonary tuberculosis from military service, routine chest roentgenograms, or routine skin tests with roentgen-ray examination of positive reactors, will probably be employed to eliminate cases of tuberculosis that have not been detected by physical examination. Because of the special equipment that will be necessary to conduct rapid roentgen-ray surveys and the time required to interpret and report the findings, it will be practicable to conduct such general tuberculosis surveys only after registrants have been inducted and sent to reception centers. Those suffering from the disease will then have to be discharged on certificate of disability. It is anticipated that such discharges can be effected within periods sufficiently short that liability for the disease and resulting compensation claims will not devolve upon the Government.

In the reception centers to which newly inducted men will be sent following acceptance by medical examining boards you will be concerned largely with the prevention and treatment of the acute infectious diseases. Measles, meningitis, influenza, pneumonia, and other air-borne diseases will constitute your greatest problem. Since the epidemiological aspects of the situation will be discussed by a subsequent speaker, I shall attempt only to review briefly the importance of such diseases in unseasoned military personnel and some of the features of treatment.

The records of the World War show that in the American Army at home and abroad during the period April 1, 1917, to December 31, 1919, there were approximately 100,000 admissions for measles, 750,000 for influenza, and 75,000 for pneumonia. Your anxiety is not only over the individual case, but it is over the aggregate number of such cases for which you may have to care at times under war conditions. You will recall that some of these diseases swept through camps at times like hurricanes from the West Indies. It was my own experience during the fall of 1918 to witness the virtual transformation of a large training camp into an immense field hospital, with most of the well occupied in caring for the sick. In this camp of 42,000 men there were during one five-week period 8,984 admissions with 499 deaths, mostly from influenza and pneumonia. Because of overwork

and massive exposure, a large proportion of the medical and nursing staff was involved. Under such conditions one will readily understand that modern hospital care, with adequate nursing attention and ideal therapeutic management, is beyond reach. In this instance even the matter of embalming the dead became a serious problem. Hundreds of oxygen tents cannot be produced overnight. Even the typing of sputum and the administration of serum to all to whom it may advantageously be given will be difficult. It is under such extreme conditions that sulfapyridine and related remedies will reach their zenith of usefulness.

Military medicine is fortunate in the development of the sulfanilamide group of synthetic drugs. Their non-deteriorating qualities, small bulk, and wide application give them an unusual adaptation to military use. Another notable advance in military medicine has been accomplished in the lyophilization of therapeutic sera. The ability of such sera to maintain their potency over protracted periods of time has made it practicable, upon the threat of hostilities, to produce large supplies and to hold them in storage for emergencies.

It is interesting to compare the mortality rate of World War pneumonia with that of today. The average death rate for all pneumonias during the war period was approximately 24 per cent. In the American Army during the five-year period 1935 to 1939 it was 5.6 per cent. Since October 1, 1939, there has been a total of 1222 cases of pneumonia in the Army and in the Civilian Conservation Corps. Only 19 of these have terminated fatally, giving a mortality rate slightly under 1.6 per cent. Although it is realized that the pneumonia of 1918 was much more virulent than that of today, the marked reduction in mortality must be attributed in considerable part to improvements in the therapy of pneumonia. From this we may reasonably anticipate that the high mortality rate of 1918 will not attend future respiratory pandemics.

Before leaving the subject of respiratory diseases, it may not be inappropriate to recall the well known fact that early diagnosis, bed rest, and generous intake of warm nourishing liquids will be determining factors in carrying many through their influenzas and milder respiratory infections without secondary pneumonias; also, that careful sterilization of eating utensils and the use of cubicles improvised with sheets or shelter halves will greatly reduce complicating cross infections.

Another problem not so spectacular but none the less important will be that of venereal disease. It is reported that during the first World War there were 400,000 cases in the British forces in France. There were 340,000 reported cases in the American Army. To state it differently, one man in every eleven acquired syphilis, gonorrhea, or chancroidal infection.

Suppression of venereal disease is difficult because it is concerned with one of man's most primitive biological urges. The situation is ordinarily approached along three lines, viz., educational, prophylactic, and punitive. Educational activities include not only the enlisted grades but also officer

personnel, in order that both may be made cognizant of the serious nature of venereal infections. Line officers should be impressed early in their careers with the importance of these diseases as causes of high noneffective rates and permanent disabilities; also, with the fact that in any organization a high venereal rate usually reflects an underlying condition of administrative and disciplinary inefficiency. Realizing that educational measures are only partially effective, provision has been made for individual mechanical and chemical prophylaxis. The Medical Department maintains prophylactic stations at all military hospitals, and at other convenient points on posts and in nearby cities, for those who will avail themselves of cleansing measures and chemical prophylaxis following intercourse.

Punitive measures aside from loss of pay while away from duty because of venereal disease are less in vogue than formerly. While severe penalties, such as confinement and extended loss of pay, had a deterrent influence on promiscuous sexual exposure, such measures undoubtedly drove many infected individuals into the hands of charlatans and patent medicine vendors. Army Regulations at present permit trial by court martial only for those who having acquired venereal disease fail to report for treatment. It is believed that under these regulations early treatment will be the rule and many will be spared the devastating results of neglected gonorrheal and syphilitic infections.

An important element in the control of venereal disease is the coöperation of local police and health officials in extra-cantonment areas. With a frank yet diplomatic approach, much can be accomplished through these agencies. We are also assisted in the matter of extracantonment sanitation by the United States Public Health Service. During the World War, officers of this national agency rendered valuable aid as consultants on local health problems, in coördinating civilian police and health activities, and in crystallizing public sentiment toward supporting these organizations. Such assistance is now being rendered in coöperation with state and local authorities in southern training areas, and plans have been formulated whereby general assistance in extracantonment sanitation will be given by the Public Health Service in time of national emergency.

The problems that have been discussed up to this point have concerned activities largely in home territory. Aside from the number of men involved and the speed with which work must be accomplished, the medical situations are those which have their counterpart in civil practice. Moreover, plans for their accomplishment can be formulated quite accurately in times of peace. When one attempts to envisage the medical service in the zone of combat, it is vastly different. As there are new styles in the peaceful arts, so are there new fashions in the arts of war. Stable warfare has become more stabilized and mobile warfare more rapid than ever before in its movement. Whether we shall face a Maginot or a Siegfried line, or encounter a blitzkrieg as exemplified by the German advance on Poland, we cannot forecast. We may be sure, however, that wherever the conflict and

whatever its character, we shall find it necessary to adapt our medical activities more closely to the teamwork of the military machine in attaining its assigned objectives. The farther we advance toward the front the more certainly, and possibly the more painfully, will this be true. Our efforts will be directed largely on the hypothesis of rendering the most aid to the greatest number, always with success against the enemy the foremost consideration. Priority will necessarily be given to the movement of troops and artillery, and to the transportation of ammunition and other combat supplies. Medical apparatus will have to be curtailed accordingly. Only the most compact and essential equipment will be available. The practice of medicine and surgery will necessarily be adapted to the altered circumstances, and the success of the medical officer will depend greatly on his ability to learn a technic which will fit the occasion. In the American Expeditionary Force in France, many eminent surgeons failed to achieve success because of their inability to function with sufficient rapidity in times of stress and to adapt their methods to the limited equipment and restricted environment necessitated by the military situation.

In the theatre of operations the medical officer will continue to encounter infectious diseases and ordinary surgical problems, but in addition he will have to deal with battle casualties and possibly diseases peculiar to trench warfare. It should be borne in mind that your obligation to the wounded soldier will begin long before you will have had an opportunity to evaluate your personal reactions to shrapnel and machine gun fire. Your responsibility will begin with the training of Medical Department enlisted men in the rudiments of surgical technic, the application of dressings, the arrest of hemorrhage, the splinting of fractures, and the movement of the wounded without further injury or aggravation of their shock. It is only with great effort that the first-aid man can be trained to give the same meticulous care on the battlefield that he would give a similar case in the atmosphere of an operating room. Among all types of battle casualties, none will suffer more from unskilled first aid than will compound fractures of the long bones. Early splinting is to be considered a life-saving measure. On the other hand, the unnecessary movement of unsplinted fractures, with resulting secondary laceration of the soft tissues, hemorrhage, and increased shock, must be bitterly condemned.

War wounds, inflicted as they are through soiled clothing and equipment and unwashed skin, are contaminated wounds. Many will develop serious complicating infections. Ordinary pyogenic organisms, tetanus, and the gas-producing anaerobes will be the chief offenders. Early debridement and immobilization will be considered just as essential as they were in the closing days of the World War. Irrigation with Dakin's solution and other chlorine antiseptics will no doubt be used, but less extensively than formerly. In the treatment of gunshot wounds, as in the management of respiratory infections, great dependence will be placed on the sulfanilamide group of drugs, with the difference, however, that here they will be used for their

prophylactic as well as their curative value. The success that has attended primary closure of badly contaminated compound fractures after debridement and topical application of sulfanilamide crystals offers great encouragement for the similar treatment of war wounds. This method of treatment may also prove to be the ideal one for perfringens and other gas-producing infections. Antitoxin and roentgen therapy, now used extensively against these infections in civil practice, are not ideal therapeutic agents for use on the battlefield.

Against tetanus outstanding progress has been made since the World War. Discussion of the subject will be left, however, to an eminent worker in that field, who will address you within the hour.

The use of transfusions in the treatment of battle casualties is another matter that occupies the thought of military surgeons. The practicability of blood banks in civil practice is well established, but to supply blood for transfusion purposes in evacuation and surgical hospitals, and other medical installations near the front lines, is a very difficult undertaking. The great problems in military practice are those of preservation and transportation. Special thought is now being given to the matter of individual containers, portable refrigerators, and airplane transport, by means of which blood can be carried to the combat area in usable condition and administered in the minimum time. The practicability of utilizing blood from civilian sources will depend largely on the geographical location of the scene of hostilities. Any comprehensive plan for the use of whole blood in the combat zone will necessitate typing of all military personnel and recording the blood types on their respective identification tags.

The Geneva Protocol of 1925 prohibiting the use of asphyxiating and poisonous gases has apparently been observed by all belligerents in the present conflict. Whether its observance is prompted as a matter of honor or by fear of reprisals is immaterial, the possibility of chemical warfare must always be considered. In view of this possibility, research looking to the development of effective treatment against chemical agents is constantly in progress. In the treatment of pulmonary irritants it is believed that helium-oxygen mixtures will find valuable application.

Psychological emergencies, vitamin deficiencies, trench feet, trench fever, nephritis, stomatitis, pediculosis, and scabies may contribute to morbidity rates. Diseases endemic in the war zone will appear. In the tropical and subtropical states of the American continent malaria and other tropical diseases will be met. Notwithstanding the highly efficient sanitary organization that has been built up in the Canal Zone, malaria still constitutes a major medical problem. Yellow fever might again be a menace in time of war. In the unexpected event of hostilities in our western United States, Rocky Mountain spotted fever, tularemia, and relapsing fever would be encountered, and should we have to meet an enemy on our southern border typhus would be a disease with which we would have to reckon.

The present war in Europe has been called a war of miscalculation. The same may be said of every war. In the Spanish-American War typhoid fever proved to be the enemy which wrought the greatest havoc. In the World War influenza appeared as the hidden foe in our midst. In the future, new conditions of warfare, new weapons, and unusual diseases will throw unexpected responsibilities upon the Medical Department. The management of these new situations will tax our resources to the utmost and we shall undoubtedly find as we have found in the past that our greatest trouble will not be in a lack of medical knowledge but, instead, it will lie in the difficulty of applying common, well-known principles of medical practice to the abnormal demands of war.

# DEVELOPMENTS IN AVIATION MEDICINE \*

By HARRY G. ARMSTRONG, Capt. M. C., U. S. Army

A HIGHLY specialized field of medical science may normally develop in two directions, either by increasing the information available in its own particular field or by broadening its scope. As a result of the tremendous growth of the aviation industry in this country during the past few years aviation medicine has shown a marked development in both of these directions which has not only brought it into a position of prominence as a medical specialty but has made it a matter of interest and importance to the general medical profession as well.

Aviation medicine may be defined as that branch of medical science which has to do with the selection, maintenance, and treatment of those who fly. The first medical studies in aviation date back to 1783 when, for the first time, both experimental animals and human subjects were sent aloft in smoke filled balloons to determine the effect of flight on the living organism. Two years later, in 1785, the American physician, Dr. John Jefferies of Boston, flew over the English Channel from England to France during which he made notable observations of the aerial environment. Subsequent to the flight of Dr. Jefferies the advances in aviation medicine have been largely confined to three rather sharply defined periods of time.

The first of these occurred between 1875 and 1878 and was the result of the work of Paul Bert, the brilliant French physiologist. Bert became interested in the effect of flight after having read accounts of the strange symptoms suffered by Glaisher and Coxwell during a series of high altitude balloon ascents. The results of Bert's studies were published in 1878 in a volume of some 1100 pages and it is astounding the amount of original data which he presented at that time. Bert's work was of interest not only to aviation but to general medicine as well, for it included much of our fundamental knowledge concerning gaseous exchanges in the body, caisson disease, and other related phenomena.

The second period of great advance in aviation medicine came about directly as a result of World War I. At the end of the first year of that conflict some startling statistics were revealed. They showed that of every 100 pilots killed during that period 2 died as the result of enemy action, 8 from defective equipment, and 90 from defects in the pilots themselves. In some instances 50 per cent of the students developed neuroses in training before ever becoming graduate pilots. It was also noted that there were whole hospital wards full of trained fliers who were uninjured, suffering from no known malady, yet completely incapacitated for flying duty. These unusual circumstances immediately attracted the attention of the best medical minds

\* Read at the Cleveland meeting of the American College of Physicians, April 1, 1940.

in each of the combatant countries engaged in the war and a great amount of medical research was devoted to these problems during the remainder of that conflict. The tremendous advances made in aviation medicine during the World War I period will not be recounted here except to mention that it emerged in this country as a recognized specialty in military medicine and that a postgraduate school of training for flight surgeons was established as a permanent part of our Army medical education system.

The third and final period of great advance in aviation medicine began in 1926 and has persisted up to the present time. In 1926 the Bureau of Air Commerce of the Department of Commerce was established for the control of civil aviation and later supplanted by the Civil Aeronautics Authority. The medical section of these agencies grew rapidly as civil aviation expanded and at the present time requires the services of approximately 700 civil physicians. In addition most of the major airlines have established their own medical departments and hence created many openings for other qualified civil physicians since it is forbidden that one physician serve both the Authority and another civil agency. Thus since 1926, when aviation medicine was confined to the military services and non-existent in civil aviation the situation has changed to the extent that civil flight surgeons now outnumber those in the Army Air Corps by a ratio of approximately 4 to 1. Although the total number of qualified flight surgeons in this country is relatively small, there is a most unusual seriousness of purpose among them as evidenced by the fact that they have their own medical association, publish and read their own medical journal, and attend their own annual medical convention.

Thus far the development of aviation medicine has been outlined only in so far as it is practiced as a specialty. It remains to show its development as a field of interest and importance to other special fields of medicine and to medicine as a whole. In order to accomplish this it is but necessary to point out that civil flight surgeons are not officially responsible for the clinical care of pilots under their supervision nor do they have any direct contact with those who travel by air. Hence, all clinical matters concerning those who fly are a responsibility of the general medical profession. To the uninformed it may appear that there is an insignificant number of these individuals or that they present no usual problems. Neither of these assumptions is true as can be shown by the following considerations.

In this country today there are over 31,000 licensed airplane pilots and 15,000 more are now in the process of being trained. The licenses of these individuals, and in many instances their livelihood, depend on the proper maintenance of their mental and physical health under the supervision of the family physician. In aviation the term physical fitness has a special significance. Naturally health is included in its general meaning but is by no means synonymous with it. Perhaps this last statement can best be emphasized by pointing out that a candidate for an air transport pilot's rating



may be free from all acute disease processes, have no obvious gross physical defects, be capable of engaging in most other occupations, and yet have over 100 disqualifying defects for flying. While it is true that many of these so called defects have no great clinical significance they have been found important in aviation and must be taken into consideration in any program of medical care if that program is to be a success.

In addition to the clinical care of pilots the general medical profession is also responsible for all medical matters with reference to civil air passengers. Altogether last year in scheduled and unscheduled passenger operations over 3,000,000 passengers were carried aloft into an unnatural environment. This is not to imply that modern air transportation is dangerous to life for it is not. It does mean, however, that our people are becoming air minded and are being exposed to new unnatural conditions, however subtle, that may affect them adversely under certain circumstances. The coming magnitude of this problem is almost unpredictable. In a recent comprehensive survey the American Institute of Public Opinion found that 42 per cent of the population of this country expressed a desire to learn to fly. That per cent amounts to 50,400,000 people. By no means is it intimated that all of these people are actually going to learn to fly but some of them are and many more will fly as passengers. Among both of these groups there are many who will be in need of medical service and guidance.

What are the medical requirements for a private pilot's license, a commercial pilot's license, an airline pilot's license? What effect does flight have on damaged hearts, on pulmonary disorders and on gastrointestinal disturbances? Are common colds, middle ear infections, or infected sinuses contraindications to flight. Should infants and the aged travel by air? Is flying safe and if so, as compared to what? What is airsickness, aero-otitis media, aeroembolism and other diseases peculiar to flight and under what conditions do these diseases develop and why? These are the questions that are being asked of the general medical profession today and those who are intelligent enough to ask are entitled to receive an intelligent answer. Especially is this so in the case of invalids or those seriously ill patients being transported by air as emergencies to take advantage of unusual skill or equipment at some distant point. In these instances the question of air transportation is often vital.

I especially wish to refer to the eight or ten million young men and boys who sincerely want to take up aviation as a career of whom probably only 1 to 2 per cent can ever qualify. It has been our experience that most of these young men consult their family physicians before appearing for their official flying examinations to determine whether or not they are physically fit to fly or to institute remedial measures for any correctable defects which they may have. In the past this procedure, unless the candidate happened to be fully qualified for flying training, has usually led to a long chain of most unfortunate circumstances due to the average physician's complete lack

of understanding of the physical and mental requirements for aviation. As mentioned above good health and fitness for flying are not synonymous. As a consequence a good clinical examination is not necessarily a good aviation examination and the former is never adequate. Based on a clinical examination alone many a young man has been assured by his family physician of his physical excellence, has spent much time and money preparing for a career in aviation, and then failed his official examination for flying. This invariably leads to a recitation by the candidate of his examination by the family physician, the wasted time and money to which he has been subjected, and invariably an accusation of incompetence against the official examiner. The latter in defending his action can leave no other conclusion in the mind of the candidate but that it was the family physician who was at fault.

There is yet one final reason why the general medical profession should interest itself in aviation medicine and this pertains to considerations of national defense. All of the major conflicts since World War I have demonstrated the fact that the air arm is not only the first to be engaged but that it is likely to be the deciding factor in any struggle. This means that the air arm must be at full strength in men and materials at the beginning of hostilities and remain so until hostilities have ceased. While the difficulties of mass production of aircraft is generally known, few persons realize that the mass training of pilots is even a more difficult one. It must also be remembered that the initiation of pilot selection and training must await the organization and training of properly qualified medical personnel. If this vital function is to be properly performed, the necessary number of civil physicians must be selected, organized, and trained before an emergency exists. For this reason alone, if for no other, the general medical profession must familiarize itself with the fundamental principles of aviation medicine to the extent that is necessary for our national defense.

Means for accomplishing this are provided by the Army Medical Department through courses of instruction to medical reserve officers and medical officers of the National Guard at the Army Air Corps' School of Aviation Medicine at Randolph Field, Texas. Evidence that this course is popular with eligible officers and that our military problem in this respect is being met is indicated by the fact that over 300 officers have already graduated from this school and about 600 more are currently under instruction.

In civil life, on the other hand, the recent great expansion of the aviation industry has created a need which our medical schools have as yet made no organized attempt to meet. In this respect they have lagged behind most of the medical schools of Europe and especially those of Germany where, for the past two years, aviation medicine has been taught to every student as a regular part of his medical education. The growing need and the growing demand for such instruction in this country have, however, not been entirely without results. The first step in this direction has already been taken by

the George Washington University School of Medicine which presented a postgraduate course in aviation ophthalmology and aviation medicine in April of this year, and at least two undergraduate schools have recently introduced lectures in this subject to their junior and senior classes.

With this encouraging beginning it does not seem unreasonable to assume that all of our undergraduate medical schools will eventually provide their students with regular courses of instruction and that other postgraduate courses in aviation medicine will be presented as rapidly as conditions permit.

# HIGH ATMOSPHERIC PRESSURES; PHYSIOLOGICAL EFFECTS OF INCREASED AND DECREASED PRESSURE; APPLICATION OF THESE FINDINGS TO CLINICAL MEDICINE \*

By A. R. BEHNKE, Lieutenant, Medical Corps, U. S. N.

THE present discussion concerns the effect of wide variations in atmospheric pressure on individuals whose usual environment has been completely altered by temporary existence in a pressure chamber, diving suit, or at high altitudes.

While these observations may be interesting primarily to workers in experimental medicine as general biological phenomena, certain physiological principles underlying the environment of the aviator and deep sea diver will be of value to physicians interested in inhalation therapy and in the utilization of pressure chambers for diagnostic and therapeutic purposes.

*Primary Pressure Phenomena in Relation to the Paranasal Sinuses and the Ear.* A consideration of pressure makes necessary the distinction between the manifestations of pressure per se, and the disturbances in gaseous equilibria in the body incident to pressure variations. Apart from disturbances in gaseous equilibria, pressure as an ecologic factor can be reduced to one-fifth of an atmosphere or increased to 15 atmospheres without demonstrable physiological effect provided that equalization of pressure takes place in the air spaces of the ear and sinuses. If, for example, the sinus and auditory tube passages are patent, the body can be subjected first to a sea water depth of 500 feet or a pressure of 240 pounds per square inch and then to an altitude of 38,000 feet equivalent to a pressure of 3 pounds per square inch without demonstrable injury.

If, on the other hand, the openings of air spaces in the ear and sinuses are occluded, then slight pressure variations in the range of 1 or 2 pounds (50 to 100 mm.) per square inch elicit painful response and induce congestion, edema, and hemorrhage in the affected tissues.

The manner in which pain is elicited may be surmised from the diagram in figure 1 which represents the body as a mass of protoplasm consisting of 70 per cent fluids and 15 per cent fat, and almost completely enveloping numerous cavities. If this body is subjected to increased pressure, every air pocket present from the smallest ethmoid cell to the air cells in the tip of the mastoid process receives air, provided that the ostia of these spaces are open. If under the same conditions the ostia are occluded, the pressure within the pneumatic space tends to remain constant while the increased

\* Read at the Cleveland meeting of the American College of Physicians, April 1, 1940.

The contents of this paper are not to be construed as an official expression of the Navy Department.

pressure force acting on the body mass and circulating blood puts tension on the cells of the lining membrane and serves to dilate blood vessels in tissue surrounding the occluded space. With reference to the sinuses it is con-

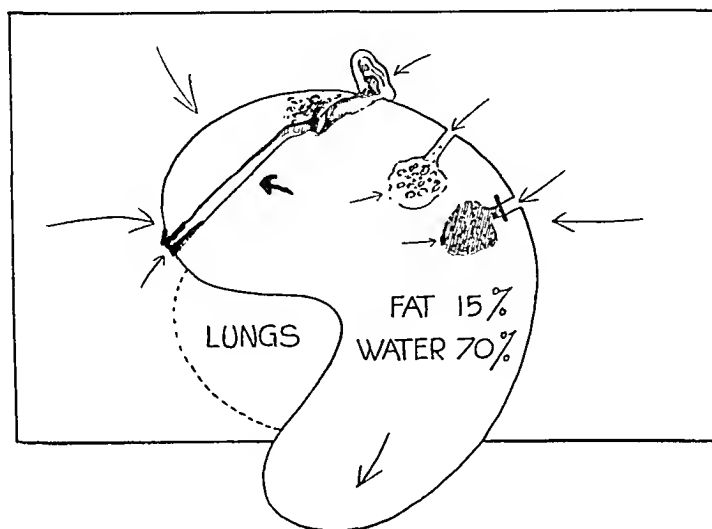


FIG. 1. Diagram to illustrate the effects of pressure on the body showing equalized pressure on the tympanic membrane and in a sinus space, and congestion and hemorrhage into a sinus space when the opening into the sinus is blocked preventing equalization of pressure.

ceivable that the congested and hemorrhagic epithelium and tunica propria tend to separate from the bony wall and to evaginate into the space of lower pressure. Pain located in and around the involved area is the concomitant symptom of the pressure force created by difference of pressure between the lining membrane and the adjacent air medium.

With reference to the ear, prior to the onset of pain as the differential pressure is increased, the blood vessels best observed within the tympanic membrane in the area of the short handle of the malleus, are seen to dilate presenting the appearance of a radiating network. Further increase in pressure ruptures vessels and elicits a painful response felt within the ear and over the mastoid area. The tympanic membrane is ruptured in the range of pressure between 5 and 10 pounds (250 to 500 mm.) per square inch.

The most important factor preventing accommodation to increased pressure and one to which individuals are predisposed, is acute or chronic upper respiratory tract infection.

The prevalence, for example, of complete or partial blockage of one or both auditory tubes is shown by the fact that out of two thousand qualified submarine personnel, 10 to 15 per cent were unable to tolerate pressure in excess of 5 or more pounds per square inch. Similar tests indicate that among the civilian population this percentage may run as high as fifty.

*The Pressure Chamber as a Therapeutic Appliance.* Utilization of pressure chambers in the submarine service makes possible a convenient method for diagnosis of congestion around the ostia and within the auditory tube

and sinus meatus. It serves also as a rapid, presumptive test of physical fitness, since individuals able to accommodate to pressure increases at the rate of 30 pounds per minute are usually free from infection of the nasopharynx. Deviations from this standard rate of pressure accommodation are usually in proportion to the severity of the disease process.

As an appliance for bringing about ventilation and drainage of ear, sinus, and pulmonary air spaces, the utilization of a pressure chamber is physiologically sound, but the therapeutic value may be limited by the consideration that immunologic factors appear to be of prime importance in the healing of pulmonary and sinus membranes rather than the mechanical factor of drainage.

In civilian life small pressure chambers might be utilized by the otolaryngologist and bronchoscopist for diagnostic and therapeutic purposes. Undoubtedly severe trauma has been inflicted on membranes by the use of suction apparatus. Suction applied to occluded sinuses in which the pressure is already decreased as a result of partial oxygen absorption, may induce drainage only at the expense of the epithelial membrane which becomes congested and hemorrhagic.

The application of positive pressure up to 10 pounds (500 mm.) per square inch in a chamber followed by subsequent release of pressure provides effective ventilation and drainage with minimum trauma.

Therapeutic appliances operating on the principle of alternate pressure fluctuations are the Drinker respirator, and various types of equipment designed to increase circulation in the extremities. It is not clear, however, that blood flow is increased in an extremity subjected to negative and positive pressure. It appears more likely that the term applied by Herrmann, "passive vascular exercise," describes the functional adjustment incident to compression and decompression, consisting essentially of a proportionately greater distribution of blood to the cutaneous area without significantly increasing blood flow to the extremity as a whole.

*Effect Of Pressure Variations on Hearing.* The problem of impairment of hearing as a result of pressure variations has received considerable attention in aviation medicine. We have observed that pressure trauma to the tympanic membrane, beginning with congestion and terminating in hemorrhage and perforation of the drum, is quickly repaired without permanent loss in auditory acuity.

Audiograms obtained on 19 deep sea divers subjected to pressure trauma over a period from 5 to 15 years show some loss in auditory acuity in the range of 4096 double vibrations. This impairment, however, does not affect hearing for spoken voice, and may reasonably be attributed to a degeneration of nerve elements in the cochlea, brought about by noise,<sup>1</sup> or incident to age.

## PART II. EFFECTS OF PRESSURE IN RELATION TO DISTURBANCES IN GASEOUS EQUILIBRIA IN THE BODY

The more important physiological phenomena incident to barometric pressure manipulation are related to the property possessed by gases of diffusing into the body when the atmospheric pressure is increased, and to the difficulty in their removal when the pressure is subsequently lowered.

*Nitrogen Absorption and Elimination Curve.* The manner in which atmospheric nitrogen diffuses into or from the body by means of the circulating blood when the air pressure fluctuates, is indicated by the graph in figure 2. Since the body solvents for nitrogen are fluid and lipid constit-

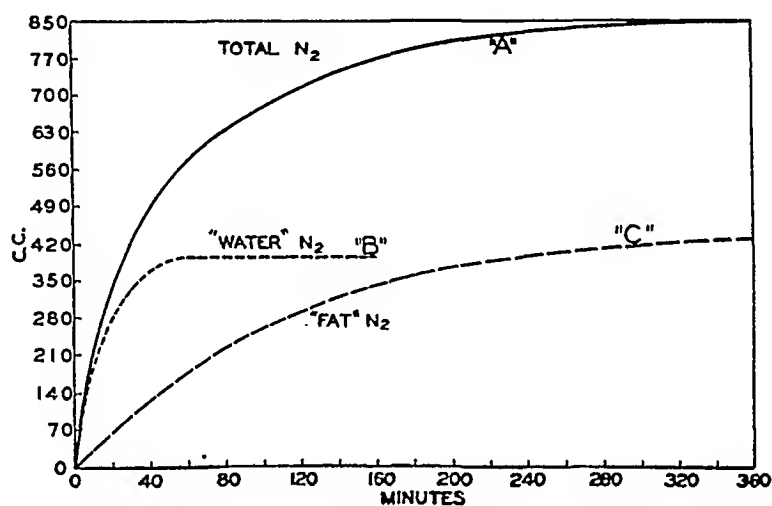


FIG. 2. Solid line shows nitrogen elimination from a young, lean man weighing about 60 kilograms. The nitrogen in the body is soluble in fat and fluids. The elimination or absorption of this nitrogen with changes in barometric pressure is represented by the hypothetical, broken-line curves on the graph. (Reproduced from the *Am. Jr. Physiol.*, 1935, cxiv, 138.)

uents of tissues, and hemoglobin, hypothetical curves "B" and "C" of figure 2 indicate probable rates of nitrogen absorption or elimination from these materials. The quantity of nitrogen diffusing into the body is therefore a function of body weight, and since the fat-water solubility ratio of nitrogen is about 5 to 1, the volume of nitrogen absorbed reflects the fat content.

We<sup>2</sup> have made approximations of the fat content of the dog's body by measuring the volume of nitrogen eliminated during the respiration of oxygen. A knowledge of the solubility coefficients of nitrogen in water and fat and the determination or estimation of the water content allow the computation of the amount of body fat.

Helium has a fat-water solubility ratio of 1.7 to 1 or approximately one-third the rate for nitrogen.<sup>3</sup> While the helium absorption curve, figure 3, is similar in shape to the curve for nitrogen, the helium content of the body

is about 45 per cent of the nitrogen content, and the elimination rate of helium is about twice the rate for nitrogen.

Exercise increases the rate of gas elimination, but the value of exercise is chiefly during the first 30 minutes, when the inert gas is diffusing from body

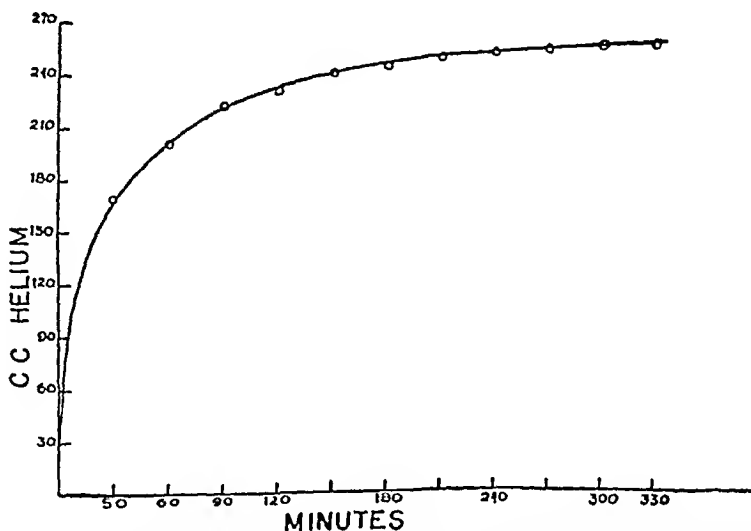


FIG. 3. Curve showing helium elimination from a young, lean man weighing 74 kilograms. Subject was previously exposed three and one-half hours to an atmosphere containing about 75 per cent helium. (Reproduced from the U. S. Nav. Med. Bull., 1938, xxxvi, 542.

fluids. Exercise does not greatly influence the elimination of inert gas from the fat depots of the body.

*Circulatory Efficiency in Relation to Rate of Gas Elimination from Tissues.* The rate of nitrogen removal is a function of cardiac output which in turn is related to metabolic mass or surface area. Small mammalian species with a comparatively large surface area in proportion to body weight eliminate excess nitrogen so rapidly from their tissues that it is difficult to produce air embolism in these animals following exposure to high pressures. For example, the rate of nitrogen transport in the dog is about double that in man.

Taking these facts into consideration it has been possible to develop an exacting test of circulatory efficiency by introducing an excess quantity of nitrogen into the body tissues during exposure in a high pressure atmosphere and then rapidly decreasing the pressure to normal.

The elimination of the excess gas from the tissues without the development of extensive air embolism upon return to normal pressure depends primarily upon effective blood flow through the tissues. Both cardiac output in relation to body weight and the adequacy of collateral circulation are the important factors preventing accumulation of air emboli in sufficient number to elicit pain in the affected parts.

*Physiological Reactions Associated with the Absorption of Nitrogen.* Beginning at an absolute pressure of about 4 atmospheres, nitrogen acts as a



narcotic to depress neuromuscular activity. At a pressure in excess of 10 atmospheres, consciousness may be lost. This remarkable property of nitrogen is consistent with the Myer-Overton hypothesis relating narcotic action to solubility in lipid substances of the central nervous system. Whether or not there is interference with carbon dioxide elimination in the denser atmosphere has not been determined.

The substitution of helium for nitrogen abolishes the narcotic effects of pressure, and an individual breathing a helium-oxygen mixture feels nearly as well at a pressure of 16 atmospheres as he does breathing air at normal barometric pressure.

It may be of interest to record that argon, like helium, possesses complete chemical inertness but unlike helium, it brings about a neuromuscular impairment and psychic depression somewhat greater in degree than does nitrogen.

These physiological studies of elementary gases apparently reveal an avenue of approach to the fundamental nature of anesthetic activity. Apart from the selective solubility of the heavier gases in lipids compared with water, the crucial consideration centers around the question of interference with oxidative systems in cells by a blanketing effect tending to limit oxygen diffusion through the cellular membrane.

*Reactions Associated with High Pressures of Oxygen.* Of the gases diffusing into the body under increased pressure, oxygen is of greatest importance. In the Navy, an important advance in the field of diving is the employment of oxygen for the prevention and treatment of compressed-air illness. During rescue and salvage operations connected with the U.S.S. Squalus disaster, the administration of oxygen constituted a life-saving measure. Oxygen, however, is toxic at higher pressures, and in the course of investigations to ascertain the value of oxygen, tolerance studies received first consideration.

At sea-level pressure, the period of time that pure oxygen can be safely breathed is a matter of controversy. Although the tolerance of the anoxemic patient may be greater than that of a healthy individual, we find that healthy men between the ages of 20 and 40 are able to breathe 99 per cent oxygen for periods not in excess of seven hours. During this tolerance period, slowing of the pulse rate and pallor are observed. If it is inhaled for a period in excess of six or seven hours, there may be a break in compensation characterized by increased depth of breathing (figure 4) suggestive of accumulation of carbon dioxide in tissues. When this break in compensation takes place the inhibitory action of oxygen on the chemoreceptors of the carotid body is replaced by a reaction typical of the stimulating effect of carbon dioxide on the respiratory center, a phenomenon of which the individual himself may not be aware.

Toxic symptoms associated with oxygen breathing and suggesting a break in compensation are flushing of the face and nausea. By reason of its recurrence when oxygen is breathed at pressures of two and one-half to

three atmospheres, nausea is regarded by us as a pathognomonic symptom of oxygen toxicity.

Pure oxygen moreover is a pulmonary irritant and numerous investigators have described the edema and pneumonia incident to oxygen inhalation in tests employing rabbits, dogs, and rats.

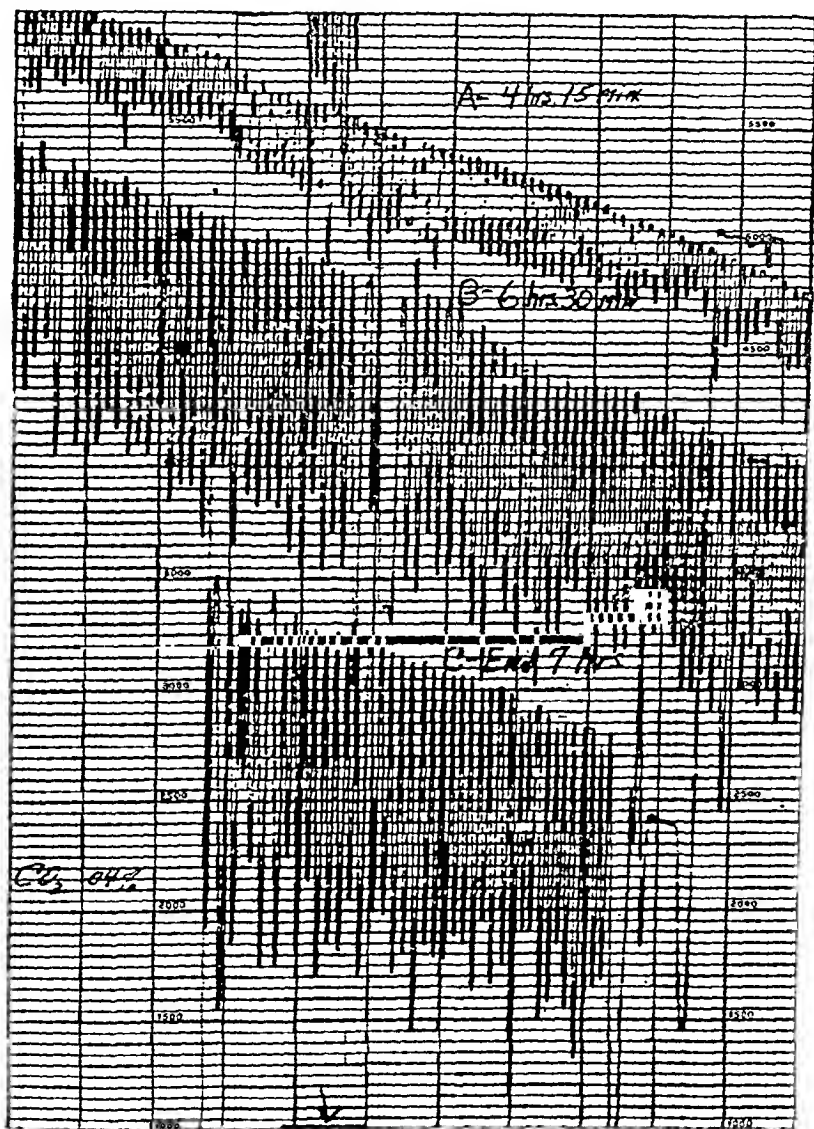


FIG. 4. (A) Amplitude of respiratory excursion after 4 hours of pure oxygen inhalation at sea level barometric pressure. (B) Amplitude of respiratory excursion 6 and one-half hours from the start of oxygen breathing.

I desire to stress the fact that our tests utilizing 99 per cent oxygen at sea level pressure are frequently terminated at the end of six hours by the complaint of substernal soreness aggravated by deep inspiration or smoking. Although auscultatory and roentgenologic examination reveal no positive findings, the symptom of substernal distress points to the irri-

tant property of pure oxygen and indicates pulmonary congestion or cardiac vasomotor spasm.

The cause of the toxic action of oxygen is not known. There is evidence that the accumulation of carbon dioxide in tissues as a result of disturbed transport incident to oxygen inhalation plays some rôle in the etiology of oxygen poisoning. In what may be termed the compensatory period, symptoms are indicative of stimulation of the sympathetic division of the autonomic nervous system. When a break in compensation occurs, the symptoms of flushing of the face and nausea in man, and a fall in blood pressure in anesthetized dogs suggest the action of a parasympathomimetic drug. The action of a histamine-like substance,<sup>6</sup> or choline derivative, explains many of the toxic symptoms associated with oxygen inhalation particularly at the higher pressures.

With regard to oxygen inhalation at a pressure of 3 atmospheres<sup>4</sup> the oxygen taken up by the blood in physical solution is sufficient to meet the tissue requirements so that oxyhemoglobin is not reduced. At this pressure oxygen can be tolerated for a period of three hours.

At a pressure of 4 atmospheres<sup>5</sup> severe convulsive seizures are observed after about 45 minutes of oxygen inhalation. These seizures are similar to epileptic convulsions except for greater intensity and longer duration. Recovery is apparently complete when air is again breathed. In dogs prolonged oxygen breathing leads to a gradual paralysis of respiration.

In these oxygen studies the importance of diffusion as a property of gases is continually manifest. For example, the oxygen content of arterial blood drawn from a peripheral vessel is lower than that of blood equilibrated with the same oxygen pressure existing in the pulmonary air due in part to the diffusion of oxygen into vascular endothelium and adjacent tissue. If Exner's law of diffusion of gases through liquids is applicable to the diffusion of gases in the body, then the velocity of diffusion is proportional to the solubility coefficient and inversely proportional to the square root of the density of the gas. Campbell<sup>7</sup> has shown that the inhalation of pure oxygen at a pressure of one atmosphere raises the pressure of oxygen in certain tissues about 30 mm.

If the oxygen pressure is increased to 4 atmospheres, the quantity of oxygen going into physical solution in the tissues is strikingly apparent. During a period of oxygen inhalation for 17 minutes an apparent increase in oxygen consumption of 159 c.c. per minute or a 55 per cent increase over a control period was observed. This increase in oxygen uptake is explained on the basis of oxygen going into solution in the tissues; approximately 2.3 volumes per cent dissolve in fluids, and 11.2 volumes per cent dissolve in fat for every 760 mm. pressure at a temperature of 38 degrees centigrade.

Clinically some of these findings are of importance. Pure oxygen because of its toxic properties may be regarded as an inhalation drug tolerated by healthy men for a period of six hours and associated with symptoms suggesting stimulation of the autonomic nervous system. It should be realized

of course, that lowering the oxygen percentage greatly extends tolerance time so that 60 per cent oxygen at sea level pressure can be breathed for periods of months.

The diffusion of oxygen into tissues emphasizes its specific value in the treatment of such conditions as acute coronary thrombosis, lessening pain and limiting cardiac damage.<sup>8</sup> The neglect shown in the utilization of oxygen in acute coronary heart disease, especially when an individual appears to be in shock from anoxia, reflects undoubtedly a lack of familiarity with inhalation therapy as an integral part of therapeutic procedure, or perhaps a lack of appreciation of the clinical pathology underlying this condition.

In such conditions as acute pulmonary edema and carbon monoxide poisoning where advantage needs to be taken of oxygen in solution, special equipment would be necessary to create high pressure atmospheres.

At 4 atmospheres' pressure, in view of questionable methods of inducing shock therapy in mental patients, as for example, asphyxiation with nitrogen, experimental oxygen inhalation to induce seizures appears to be justified.

### PART III. OBSERVATIONS RELATING TO NITROGEN BUBBLE FORMATION FOLLOWING EXPOSURE TO HIGH BAROMETRIC PRESSURES

Of great interest and worthy of more extensive study are the responses brought about by the presence of gas bubbles in the blood stream. In no other way perhaps, are weaknesses in the circulatory system made more apparent than by the presence of small air bubbles.

In the Navy one of our problems is to protect deep-sea divers from developing extensive air embolism following too rapid decompression from high pressure atmospheres. Aviators in rapid ascents to high altitudes are also exposed to the hazard of air embolism.

Although bubbles evacuated in the blood of aviators during rapid ascents to high altitudes contain high percentages of carbon dioxide, yet it is the high partial pressure of nitrogen in the body in relation to the external pressure that initiates bubble formation giving rise to the depressive fatigue, and at times pain incident to high altitude flights. Insofar as the problem of bubble formation is concerned, an ascent by an aviator from sea-level (1 atmosphere) to an altitude of 33,800 feet (0.25 atm.) is equivalent to an ascent by a diver from a depth of 100 feet (4 atmospheres) to the surface (1 atm.).

Bubble formation in divers is a common occurrence following decompression. In small quantities bubbles produce nothing more than pruritus usually more intense in the lobes of the ear and over the chest and abdomen. If the skin is chilled, the attendant vasoconstriction and slowed circulation enhance the liberation of gas in bubble form. Frequently a transient abdominal rash is observed which may closely resemble a macular eruption of secondary syphilis.

I believe that these symptoms are indicative of intravascular rather than

cellular or intercellular bubble formation. The disappearance of the skin rash, for example, is frequently too rapid to be accounted for by the presence of extravascular bubbles. In dogs rapidly decompressed from high pressures the veins may be filled with gas bubbles, while the lymphatic vessels are free from bubbles. Further, the remarkable amelioration of symptoms brought about by recompression without residual damage strongly supports circulatory impairment as the prime cause of symptoms rather than pressure on cells exerted by free gas.

Bubbles when first formed circulate through the whole vascular system and accumulate later in the large veins. Both pulmonary and peripheral capillary beds serve to trap the free gas. In the pulmonary vascular bed gas emboli increase resistance to the contractions of the right ventricle. Pulmonary gas emboli cause substernal and precordial distress aggravated by deep inspiration which elicits the cough reflex.

The substernal distress appearing several hours after exposure in compressed air is frequently accompanied by an exhausting fatigue which suggests an impaired venous return of blood to the right side of the heart. The wide dissemination of gas emboli in the pulmonary bed increases substernal distress and brings about asphyxia by interference with alveolar aeration and oxygenation of blood. The descriptive term, "chokes," has been applied by caisson workers to the symptoms induced by pulmonary embolism.

Since impairment of blood flow gives rise to the symptoms of compressed-air illness, it may be logically inferred that those parts of the body affected first by gas emboli would be areas of deficient circulation as the region of the joints and certain areas of the spinal cord. This inference is verified by our clinical findings. The region of the knee is most frequently involved and the sensation of pain is felt in the head of the tibia or the distal end of the femur. The term "bends" has been applied by divers and caisson workers to pains in the extremities. A feeling of stiffness may precede the onset of pain. In the extremities areas of previous injury as the site of an old fracture may be the first to give rise to pain. While pain around the joints usually follows long exposure in compressed air suggesting the liberation of free nitrogen gas in vessels within bone marrow, the symptom also appears after short exposures indicating susceptibility of joints or the distal ends of long bones to deprivation of blood supply by gas emboli disseminated from the general circulation.

The area in the spinal cord most frequently affected by embolic ischemia is the lower dorsal and upper lumbar portions giving rise to weakness of the lower extremities, spastic paraplegia, and genito-urinary impairment. Typical of the sudden onset of symptoms referable to the spinal cord is the history of a diver who remained in excellent condition for a period of four hours following a long exposure under pressure equivalent to a depth of 60 feet. No sooner had a notation been made in his record to the effect that he appeared to be in excellent health, than it was reported that his legs were

numb and unable to support his weight. No other symptoms were present and immediate and prolonged recompression brought about complete recovery.

Clinical conditions manifesting symptoms similar to those associated with the presence of air emboli in the spinal cord are tabes dorsalis, and arteriosclerosis of the terminal aorta involving the lumbar segmental arteries. Reichert et al.<sup>12</sup> described the condition of four patients who exhibited weakness of the thighs on exertion, not accompanied by pain and associated with normal pulsation of the femoral arteries. These patients showed, however, extensive calcification of the terminal aorta. Reichert confirmed his observations by producing a similar syndrome in dogs following ligation of the lumbar segmental arteries.

The effect of interference with the blood supply to tissues by intravascular bubble formation in young, healthy, vigorous men simulates the symptoms associated with the aged or with individuals afflicted with arteriosclerosis or syphilitic arterial disease.

Fortunately, incipient lesions incident to ischemia induced by gas emboli undergo rapid resolution if blood flow is promptly restored by the application of adequate recompression.

In brief, we desire to stress the fact that air embolism following decompression from high pressure atmospheres or decompression from normal atmospheric pressure to sub-stratosphere levels, affects most frequently areas prone to injury by reason of poor blood supply. The cerebrum, cerebellum, and pons usually escape serious injury even when the emboli are widely distributed; i.e., paralysis of cerebral origin is, for example, rare. The viscera also do not show residual damage undoubtedly because they possess excellent collateral circulation.

#### SUMMARY

1. The physiological effects of increased pressure up to 16 atmospheres or pressure decreased to one-fifth atmosphere fall into two groups, (a) effects of pressure per se, and (b) phenomena associated with disturbances in gaseous equilibria.

2. The primary pressure effects are observed if auditory tube and sinus openings are not patent. Obstruction creates a differential pressure between tissues and the adjacent air spaces. Pain is elicited as a diagnostic symptom and is associated with congestion and hemorrhage of membranes lining the occluded spaces.

3. Of the gases absorbed under pressure, (a) atmospheric nitrogen exerts a narcotic effect, minimized or abolished by the substitution of helium; (b) pure oxygen at atmospheric pressure elicits symptoms of bronchial irritation or vasomotor spasm if breathed for six or seven hours, and at a pressure of four atmospheres induces convulsive seizures followed by apparently complete recovery.

4. Observations are presented describing the effects of air emboli formed following decompression from high pressure atmospheres, the emboli affecting those parts of the body having poor circulation.

5. The clinical significance of the data is discussed particularly with reference to the use of a pressure chamber for diagnostic purposes, and to the value of certain aspects of oxygen therapy.

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# EPIDEMIOLOGY IN THE ARMY \*

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## I. INTRODUCTION

THE task of safeguarding the health of the American soldier, especially during war, is a responsibility of the entire medical profession of the United States. It has always been the policy of our peace-loving nation to maintain only a small regular army, capable of rapid expansion during emergencies by the addition of civilian soldiers. Likewise, the medical care afforded the troops during each of our major wars has been provided largely by the mobilized doctors of the country; and the quality of this service has reflected the status of medical development at the time.

With this responsibility in mind, the present chaotic international situation is sufficient to cause the physicians of America to give serious consideration to the medical problems which will arise should the nation again be forced to mobilize. Undoubtedly, one of the most important of these problems will be the prevention of communicable diseases, especially the infections, which frequently occur among troops in epidemic form.

In this talk we are concerned primarily with military epidemiology in its broader sense. After indicating some of the characteristics of the soldier and the dangers to which he may be exposed during peace, mobilization, and war, we will consider certain groups of diseases against which he can be protected, and others for which effective control methods are still urgently needed.

## II. PHYSICAL CHARACTERISTICS OF THE AMERICAN SOLDIER

At the time of his enlistment the American soldier is a healthy young man between 18 and 35 years of age. Because of the physical standards required for his selection, he is relatively free from disabling anatomical defects and disease. During the World War, when more than 4 million men were mobilized, about 92 per cent were white, and the others were either colored or natives of our colonial possessions. As the Army is recruited from all sections of the country and from every social group, its personnel is made up of a mixture of all the races and classes included in our heterogeneous population. The magnitude of the task of protecting the health of these individuals can be visualized by reviewing some of the hazards peculiar to military life and evaluating the medical facilities now available for meeting them.

\* Read at the Cleveland meeting of the American College of Physicians, April 1, 1940.



### III. THE HAZARDS OF MILITARY LIFE

These hazards may be conveniently separated into three categories, namely: (1) those incident to peacetime service in the Regular Army; (2) those which arise during mobilization, and (3) those associated with actual warfare.

(1) *Peacetime Service in the Regular Army.* The peacetime life of the Regular Army soldier probably is as safe, if not safer, than that of his brother in civil life. After being carefully selected, he is housed in modern barracks, fed a balanced diet of wholesome food, and forced to take adequate supervised physical exercise. He is trained in personal hygiene and required to carry out its principles. Finally, his health is constantly guarded by medical officers, and in case of illness or accident he immediately receives treatment in a modern Army hospital.

During 1938, when there were 182,000 men in the Army, the annual rate per 1000 for admissions to sick report was only 542, and the death rate was 3.2. These low rates indicate the satisfactory health conditions which now exist in the Regular Army.

(2) *The Hazards of Mobilization.* When mobilization occurs every effort is made to expand and continue the existing medical facilities. However, the rapid accumulation of recruits from all parts of the country and their concentration in temporary camps introduce new conditions which favor the development of such diseases as are transmitted through crowding and intimate contact among individuals. These unseasoned young men, possessing various degrees of susceptibility to infection, bring with them and introduce into the newly congregated groups an infinite assortment of the pathogenic organisms indigenous to their home communities. Such ideal conditions for herd infection have frequently resulted in epidemics of the diseases which are transmitted through the exchange of respiratory secretions. Naturally, the prevention of such outbreaks is a matter of great military importance.

(3) *The Hazards of Actual Warfare.* During actual warfare the soldier is not only faced with the danger of injury and death due to battle, but he continues to be exposed to infectious diseases, some of which may attack with such epidemic force as to jeopardize the attainment of military objectives. As the nature and severity of these infections depend on many complex factors, there has been considerable variation in the epidemics associated with our different wars. Yet, considered as a whole, disease has always been a more important factor than injury in the production of war casualties.

### IV. PROPORTION OF CASUALTIES PRODUCED BY DISEASE AND BY BATTLE INJURIES

Beginning with the American Revolution there has been a progressive improvement in the medical care afforded the sick and wounded of the

United States Army. However, in each of our wars epidemics have occurred, and the morbidity and mortality rates for disease have been higher than those attributed to battle. In the Mexican War (1846-8), for example, the disease deaths were seven times as numerous as those due to wounds. During the Civil War there were about 6 million admissions for disease, and the reported causes of death were: "unknown," 24,000; "battle injuries," 94,000; and "disease," 186,000. This result is not surprising, for at that time few of the microscopic agents of disease had been discovered and the microbiological sciences were unknown.

In 1898, when the United States engaged in its brief war with Spain, both bacteriology and protozoölogy were developing rapidly. The microorganisms responsible for a number of specific diseases had been discovered, and during that year Shiga incriminated the dysentery bacillus. However, the epidemiology of many infections was still imperfectly understood, and therefore military hygiene and sanitation were neither well developed nor generally appreciated. Again the infections, especially typhoid, caused a large proportion of the casualties, and for every man killed in battle seven died of disease.

Two decades later our Army entered the World War better prepared to meet the challenge of certain of the infectious diseases. Between April 1917 and December 1919 about 4 million men were mobilized—a larger army than had participated in any previous war in the history of man. In this enormous force the casualty rates for total diseases were considerably lower than in previous wars, there being 50,000 deaths due to battle and 58,000 attributed to disease. However, the respiratory infections were prevalent, and influenza appeared in virulent epidemic form.

Thus past experience shows that the activities of a military force may be seriously hampered by any one of a variety of diseases, and therefore it is difficult to predict the specific problems that may arise during a future emergency.

## V. THE DISEASES OF MOBILIZATION AND WAR

In making plans for the future one must consider all the important diseases that might interfere with the efficiency of troops during either mobilization or war. Naturally, the soldier is subject to most of the infirmities of mankind, but because of his age and the manner of his selection, he is less susceptible to the so-called endogenous diseases than to those which are exogenous in origin. The latter group includes various conditions associated with inanimate agents as, for example, the vitamin deficiencies, which have been eliminated during the present century by the application of our modern knowledge of nutrition and mess management. Of much greater significance are the specific diseases caused by living agents, many of which have ravaged the armies of man since the dawn of history. The scope of our future problems in military epidemiology may be visualized by briefly con-

sidering certain of these infections grouped loosely according to the methods of their transmission.

(1) *Wound Infections.* Since the time of Paré, when the wounded received little or no attention except that afforded by their comrades or female camp followers, there has been a progressive improvement in the treatment of wounds. The development of modern antiseptic surgery has resulted in a spectacular decrease in the morbidity and mortality formerly reported for wound infections. Nevertheless, such infections will continue to occur, and certain types, particularly those due to pyogenic organisms and the *Clostridia*, will always constitute a military hazard.

At present there is reason to hope that the pyogenic infections may be further reduced by the prophylactic use of sulfanilamide or some other chemotherapeutic agent; and that the use of tetanus toxoid for active immunization may eliminate certain difficulties inherent in the present method of prophylaxis. More satisfactory procedures are still required for the prevention of gas gangrene and other anaerobic infections of wounds.

(2) *Gastrointestinal Infections.* The gastrointestinal diseases, transmitted through the ingestion of contaminated food or drink, were long considered of primary military importance. During past wars many fine armies were crippled or destroyed by typhoid, the paratyphoids, dysenteries, and cholera. The evolution of methods for providing troops with safe food and water caused a material decrease in the enteric diseases, and Russell's development of an effective vaccine has practically eliminated typhoid from the U. S. Army.

For example, the diarrheal infections, which caused one-fourth of the disease casualties of the Civil War, were relatively unimportant during the World War, the admissions being only 22 per 1000 and deaths 0.07.

As to typhoid, Vedder stated that: "In 1898, during the Spanish American War the typhoid admission rate was 141 per 1000 and the death rate was 14. If this experience had been repeated during the World War, there would have been 560,000 cases and 56,000 deaths." In fact, during the latter war typhoid caused only 1529 primary admissions. (The admission rate was 0.37 and the death rate 0.05 per 1000.)

(3) *Venereal Infections.* Increased prevalence of the venereal diseases has long been associated with periods of military activity. This has been due in part to the fact that young men, whether congregated in barracks or elsewhere, fail to qualify biologically as "plaster saints," and in part to the mass hysteria with which war usually afflicts both men and women.

These diseases are of considerable military importance because of the disability which they cause and the time lost during treatment. Since the American Revolution, the Army has employed various methods in the attempt to reduce their incidence. These have included: loss of pay during hospitalization, trial by court-martial for misconduct, and the compulsory use of prophylactic measures. During the World War the admission rate

for venereal infections was almost 87 per 1000, or one-tenth of the total disease admissions; and they ranked second only to influenza as a cause of lost time. The prophylactic measures now in use are believed to be of definite value, but there is need for improvement.

(4) *Respiratory Infections.* The most important diseases encountered during the last war were those transmitted by personal contact and through the inhalation of infected droplets into the respiratory tract. Some of these, including influenza, the common cold, the pneumonias, diphtheria, scarlet fever, measles, mumps, and meningitis, occurred in epidemic form.

Three of the respiratory tract diseases, namely, influenza, bronchitis, and pneumonia, were responsible for over a million admissions to hospital and 44,000 deaths. This represented one-third of the total admissions for disease and 80 per cent of the disease deaths. Influenza alone caused about 800,000 admissions and 24,600 deaths. Recent progress made in studies dealing with influenza, the common cold, and pneumonia suggests that eventually it may be possible to immunize troops against certain of these infections. It also seems probable that the use of chemotherapeutic agents may cause a reduction in their mortality.

Diphtheria and scarlet fever are less important as military hazards, and specific biologicals are available for their prevention and treatment, but their epidemic appearance among troops may give rise to annoying and perplexing administrative problems. Similar problems arise with the occurrence of measles, of which there were 98,000 cases during the World War, and of mumps, which though numerically unimportant ranked third as a cause of lost time. The control of meningococcus meningitis, which was relatively infrequent but an important cause of death, is not considered satisfactory. In fact, it appears that the elaborate meningococcus carrier surveys which were conducted during the war may have been useless. The effectiveness of vaccination against smallpox is indicated by the fact that during the last war the incidence of this disease was negligible (0.5 per 1000) and there were no deaths.

(5) *Insect-Borne Infections.* The insect-borne diseases probably have been just as important as the intestinal or respiratory infections in shaping the twisted course of human history. Since the earliest times armies operating in countries afflicted with endemic malaria, yellow fever, typhus fever, or plague have been attacked and crippled by epidemics of these diseases.

Our World War experience fails to indicate their potential military significance. The admission rate for malarial fevers was 3.7 per 1000, with practically no deaths; there were only two cases of typhus, and both yellow fever and plague failed to appear. Unfortunately, this low incidence cannot be ascribed to the use of specific control methods, as it was due largely to chance or the absence of these diseases from the regions occupied. In the future we may not be so fortunate and, therefore, better methods should be developed for the control of insect-borne diseases in the field. Theoretically this is possible, since much information concerning the mechanism of their

transmission is now available. Practically it is difficult, because troops engaged in field duties have little or no time for insect control, and prophylaxis must depend on methods which protect soldiers against the bites of infected vectors or the organisms which they transmit.

In malarious regions troops can be kept on their feet and free from clinical malaria by the daily prophylactic use of quinine, but this drug simply delays the appearance of the disease during its use and does not prevent infection. Atabrin, plasmochin, and other chemicals are now being investigated in the search for a better field prophylactic. Since the discovery of jungle yellow fever in South America, this disease is again recognized as a serious menace to troops, and it is hoped that the vaccine now being tested in Brazil and elsewhere will be found to be effective. Various plague vaccines have been proposed and tried, but their specific military value has not been demonstrated. The delousing of troops, which was employed during the World War, is not considered adequate for the prevention of typhus. Therefore, the new rickettsia vaccines now being tested are of great interest to those concerned with military preventive medicine.

In concluding this talk it is desired to emphasize the following facts:

(1) Since the middle of the last century there has been a remarkable improvement in the medical care afforded the American soldier, and it is now possible to protect him against certain diseases which formerly menaced his health and life.

(2) Beginning with the pioneer discoveries of Pasteur, Koch, and Lister, each step in this tedious advance in military medicine has been made possible by some new fundamental truth discovered through the painstaking efforts of a host of investigators working in the laboratories and hospitals of the world.

(3) There are still many serious diseases against which we are unable to protect troops, and the urgent need for effective control methods is a challenge not only to the Medical Corps of the Regular Army, but to every physician in the United States.

(4) When one considers the satisfactory results obtained through the enormous expenditures so wisely made for the development of more effective munitions, and when one realizes that every improvement in disease control which we now enjoy is the direct result of scientific investigation, it seems obvious that a comprehensive program for research in military preventive medicine deserves an important place in our plans for national defense.

## RESULTS OF THE USE OF EXTRACT OF THE INTESTINAL MUCOSA IN THE TREAT- MENT OF VASOMOTOR RHINITIS\*

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For many years it has been suspected that histamine has a rôle in the allergic reaction. If this is true, a substance having the ability to detoxify histamine would seem to have useful therapeutic possibilities in the treatment of allergic conditions. An intestinal extract † said to have such detoxifying properties against histamine, has been supplied to us for therapeutic trial in the treatment of allergic conditions and this paper deals with our preliminary clinical observations in the use of this product.

Only a few of many important experimental and clinical observations on the rôle of histamine in relation to allergy and anaphylaxis and on the histamine-detoxifying extract (histaminase) will be referred to in this brief report. In 1910, Dale and Laidlaw reported that the injection of a small amount of histamine intravenously into a guinea pig would cause symptoms and postmortem findings similar to those described by other workers when they injected peptone into the circulatory system of a peptone sensitized guinea-pig. Lewis and Grant, in 1924, noted that stroking the skin of a normal person or especially of one who had factitious urticaria would produce a cutaneous response similar to the response to histamine when this substance is punctured into the skin. These investigators concluded that injury to the skin liberated a chemical substance which had a histamine-like action that was responsible for the formation of a wheal by its effect on the vessels and nerves.

Another significant observation was that of Hare who demonstrated, in 1926, that the reaction of the skin of allergic patients to specific proteins was almost identical with the cutaneous response to histamine. These and other similar findings suggest that histamine plays some part in conditions of allergy and anaphylaxis. Also these findings support the views of Lewis and Dale each of whom had been led to believe that the allergic reaction was due to the interaction of the antigen and antibody in or on the cells and that this interaction caused the formation or liberation of either histamine or of a histamine-like substance which, in turn, was responsible for the symptoms owing to direct action on the cells of the body. The isolation of the H-substance from the blood of rabbits and its identification as histamine by Code and Ing and the subsequent demonstration by Code that histamine is to be found in comparatively large quantities during anaphylaxis in certain ani-

\* Submitted for publication February 13, 1939.

† The extract used in this study was courteously supplied by the Department of Medical Research, Winthrop Chemical Co.

mals support the previous hypotheses that in conditions of anaphylaxis and allergy histamine plays an important part.

In 1929, Best demonstrated the presence of a histamine-inactivating material in the lung and in other tissues of the animal body. Further information concerning the action, properties and distribution of this substance was presented by Best and McHenry in 1930, who then found that in dogs the histamine-inactivating material was found in largest amounts in the small intestine and kidneys, that a moderate amount was present in the lungs and blood and that very little was present in the skeletal muscles, liver and spleen. Because this substance seemed to possess many of the characteristics of an enzyme, Best and McHenry gave it the name "histaminase." This substance, they thought, exerted its enzymatic action on the histamine molecule by rupturing the iminazole ring, thus bringing about a change such as to cause the histamine to lose its usual physiologic action.

In recent years there has been available in Europe a preparation which is an intestinal extract and which has properties said to be similar to those of the "histaminase" of Best and McHenry. Reference to a great number and variety of conditions, both allergic and nonallergic which have been treated with this substance with startling and almost uniformly good results may be found in German literature. Roth and Horton of The Mayo Clinic reported on March 3, 1937, very favorable results in the treatment of patients hypersensitive to cold with this preparation, and more recently Foshay and Hagebusch stated that this substance will lessen materially the severity and shorten the duration of serum sickness.

The use of this intestinal extract therapeutically for vasomotor rhinitis was reported first by Adelsberger in October, 1937. He reported very favorable results in the treatment of a group of 39 allergic patients, eight of whom had allergic rhinitis. Five of the latter were cured completely, the condition of one patient was improved and two were unable to notice any change in their symptoms. Although the substance was used by us occasionally in the treatment of a number of other allergic conditions, this report concerns our experience with its use in the treatment of vasomotor rhinitis only.

Vasomotor rhinitis was chosen for study for several reasons. It is a common condition and the nasal membranes could be observed before and after the substance was administered. Therefore, this condition gave an opportunity for deriving objective as well as subjective evidence of the effect of the substance administered. Also, certain cases of vasomotor rhinitis are encountered which are due to or are suspected of being due to sensitivity to food and because the preparation is an intestinal extract, it was felt that it might be more effective in cases of allergy to food than in cases of allergy caused by inhalants or physical agents. There are many cases of vasomotor rhinitis, however, in which it is impossible to prove that allergy is an etiologic factor, although in all other respects they appear to be identical with allergic rhinitis. We are well aware of the difficulties of drawing con-

clusions relative to the effectiveness of any remedy in the treatment of a condition such as vasomotor rhinitis or, indeed, of any other allergic condition. We know full well that in such cases spontaneous remissions of symptoms occur for no known reason and that there is a tendency for uncomplicated vasomotor rhinitis to improve over a sufficient period of time. Having borne these facts in mind, we feel that the results to be reported are at least conservative, if not conclusive.

### PROCEDURE

The routine procedure consisted of having the patient take orally one or two (usually two) tablets of the extract ten minutes before each meal.\* In cases in which this amount was felt to be ineffective, the dose was raised to four tablets before each meal before discontinuing its use altogether. Because the supply of material was limited, the administration was not continued beyond seven to fourteen days among those patients who failed to be relieved by the aforementioned procedure. An attempt has been made to keep those patients who were relieved supplied with quantities of the material sufficient to keep them comfortable.

Twenty-nine patients who had vasomotor rhinitis were observed in this study. In 19 of the cases there was sufficient evidence in the results of cutaneous tests and in the clinical histories to suggest that the nasal symptoms were aggravated by the ingestion of specific foods. The remaining ten patients had vasomotor rhinitis which had been resistant to other forms of treatment. Nasal obstruction was constant in 19 cases and intermittent in 10 cases. Eight patients were males, 21 were females and their ages ranged from 10 to 59 years.

Of the 29 patients, 12 (41.3 per cent) were relieved of the nasal obstruction, watery discharge and sneezing. Of the patients who gained relief, a definite improvement in the appearance of the nasal membranes could be seen. The condition of four patients (13.7 per cent) apparently was improved, but not to the extent experienced by the 12 previously mentioned. The remaining 13 patients (44.8 per cent) did not receive appreciable relief of the nasal symptoms. In certain of the cases in which relief seemed to occur at first, subsequent inquiry revealed that, later, benefit failed to be obtained from the treatment. Failures in the use of a remedy are usually more accurately evaluated than degrees of improvement. In these instances, however, in which the dosage and duration of administration are not well standardized and in which the material administered varies in potency, the evaluation of results may not be entirely accurate. Before considering the question of variation of the material used, the records of three cases in which benefit was derived from the use of this extract will be reviewed.

\*Each tablet represents five histamine detoxicating units. One unit represents the quantity of extract which is capable of detoxicating 1 mg. of histamine in 24 hours at a temperature of 37° C.



## CASE REPORTS

*Case 1.* A woman, aged 24 years, complained of symptoms of vasomotor rhinitis and mild asthmatic wheezing. She began treatment with the intestinal extract in March, 1937. The typical symptoms of vasomotor rhinitis began in 1933 and after a study from the point of view of allergy by her home physician, followed by the prescribing of a dietary regimen which involved a process of elimination of certain food-stuffs together with the administration of calcium, her condition improved; but later the remedial measures became ineffective. In September, 1936, nasal ionization elsewhere resulted in almost complete relief for 12 weeks. The symptoms gradually returned to their previous degree of severity and there were never periods longer than 12 hours during which she was free of symptoms. At that time there did not seem to be any relation between the nasal symptoms and ingestion of any special foods. Asthmatic wheezing occurred during exposure to cold and after moderate exercise.

Physical examination was essentially negative except for bilateral, nasal obstruction. The nasal mucous membranes were characteristic of the allergic type. Roentgenologic examination of the sinuses showed evidence suggestive of chronic pansinusitis with thickened membranes, secretion in the left antrum and polyps in the left side of the nose. Roentgenologic examination of the thorax gave negative results. An eosinophilia of 10.5 per cent was present. All cutaneous tests with air-borne and food allergens gave negative results. The administration of two tablets of the extract ten minutes before each meal brought about remarkable relief after the first few days and other types of treatment were not required to keep the patient comfortable, for the period of several months during which we were able to follow her case. Relapses occurred when the administration of the preparation was discontinued.

*Case 2.* A Jewess, aged 38 years, came to the clinic for the first time in 1933 and complained of constant nasal obstruction, copious, thick, yellowish, purulent nasal discharge, frequent frontal headaches and many attacks of bronchitis associated with moderately severe asthma each winter since the age of 18 years. An operation on the tonsils had been performed three times. She had had a bilateral external operation on the maxillary sinuses in 1926. Examination revealed evidence of widespread infection of the paranasal sinuses. Allergic studies gave negative results. Local treatment to the nasal membranes gave but temporary relief.

On November 4, 1938, the patient returned and complained that nasal symptoms were not relieved but that the bronchitis and asthma had been relieved greatly after she had spent the intervening winters in Florida. She had observed that ingestion of spaghetti, sago, tapioca, salmon and salted herring would aggravate the nasal obstruction and discharge. These foods had been eliminated from her diet. Nasal examination revealed that the mucous membranes were full, edematous and pale and that a heavy mucoid secretion was present in each nostril. The inferior turbinates were hypertrophic and they blocked the nasal passages. Washings from each maxillary sinus did not show evidence of infection. Allergic cutaneous tests for inhalants and foods were repeated, but all gave negative results except for a reaction to beef which was graded 1 plus. Roentgenologic examination of the thorax gave negative results.

The patient was given two tablets of the intestinal extract before each meal and after the first day "wonderful" improvement was noticed. The nasal discharge and obstruction had disappeared by the second day of treatment and the patient stated that she had not been able to breathe so well in 20 years. On the third day, the examination showed that the nasal passages were open, the mucous membranes were less edematous than formerly, were dusky in color and the secretions appeared normal. She has remained free of symptoms while using the extract.

*Case 3.* In January, 1937, a woman, aged 38 years, began treatment with the intestinal extract. She had been a patient at the clinic frequently since 1934 for treatment of nonseasonal allergic rhinitis and ragweed hay fever. For many years

she had complained of nasal obstruction, watery discharge and frequent sneezing, but recently these symptoms had become more distressing than formerly. She would awaken about four o'clock in the morning and would sneeze for two to three hours. Relief was not experienced in different bedrooms, in a pollen-free room or in different parts of the United States and Canada, but she was entirely free of symptoms in Europe and on board ship. The symptoms returned a few hours after her arrival in New York. Ingestion of lettuce, peas and oranges was known to increase the severity of the nasal symptoms. Amytal would cause severe itching and generalized hives. A carefully controlled diet based on a process of elimination of suspected foodstuffs under the supervision of a dietitian and desensitization to pollens had failed to give relief. Cutaneous allergic tests for manifestations toward inhalants and foods revealed many positive results to each group. The greatest reactions were obtained by testing with ragweed, red root, maple, poplar, whole wheat, crab, lobster, tea, navy beans, tomato, turnip, parsnip and lettuce. The administration of three to six tablets of the intestinal extract the day before a meal which contained foods known to aggravate her nasal symptoms never failed to control the distress. When administration of the preparation is discontinued the symptoms return.

### COMMENT

Certain inconsistencies in the reactions of patients to this material were noted almost from the first. Some individuals already referred to seemed benefited at first and later did not receive benefit. Other individuals who seemed definitely benefited by the extract prepared for oral use, were not benefited when given a similar preparation prepared for intramuscular use, although Foshay and Hagebusch stated subsequently that they had found the latter preparation equally as efficient in relieving serum sickness as the oral preparation. This variation in material was apparent to one of the patients who was able to distinguish between tablets from different consignments by their effect on his symptoms. At our request, Dr. Charles Code at the Institute for Experimental Medicine tested in vitro one consignment of the material for its histamine-destroying properties and no such effect was found. There is, then, both experimental and clinical evidence to suggest that a variation in the potency of the intestinal extract exists and that the results of this study and, perhaps, the results of other series of observations should reflect such variations.

It seems obvious that conclusions may not be drawn at this time from this study. Although many of the patients selected for treatment were not benefited, the relief experienced by other individuals seemed so definite and so remarkable that the use and further study of this product in cases of vasomotor rhinitis and allergic conditions of known or unknown etiology are warranted. Also, definite evidence is not forthcoming from our studies that allergic rhinitis due to ingestion of foods responds better to the administration of the extract than does allergic rhinitis due to other causes. We are still unable to predict which patients who have vasomotor rhinitis will obtain relief from the use of this material. The matter of dosage remains unsettled. Information is lacking as to how or where the material is absorbed from the intestinal tract and the time necessary for its action is not known.

Neither is there evidence that the benefit, when it occurs, is attributable to the activity or content of an enzyme, although at the present time this hypothesis offers the best explanation of the action of the extract. Although the use of this intestinal extract in the treatment of vasomotor rhinitis seems to have definite promise, a more accurate clinical evaluation of this product must await additional work which is in progress.

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# CLINICAL DESENSITIZATION TO WHEAT BY USE OF AN ACETYLCHOLINE DERIVATIVE\*

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THE focal reactions which result in the clinical syndromes of bronchial asthma, vasomotor rhinitis, eczema, urticaria and angioneurotic edema occur in tissue which is supplied by the cholinergic division of the autonomic nervous system. The peripheral mechanism which produces these symptoms may be initiated or exaggerated by different stimuli such as the antigen-antibody reaction of allergy, local irritation, infection, autonomic nervous reflex, and emotion or psychogenic stimuli. It is frequently possible to reproduce at will the particular symptom to which a hypersensitive individual is susceptible by small doses of acetylcholine or its derivatives. Hundreds of methods of altering the status quo of the bodily reactions resulting at least in temporary alleviation of the above symptoms in a few individuals have been reported. The state of local tissue reactivity may also be altered in selected individuals and the symptoms controlled by repeated cholinergic stimulation. This method of therapy is particularly significant because it is in accord with the new knowledge of the chemical transmission of nerve impulse, a concept which will influence future study of many functional disorders.

In a group of seven patients who were proved to be allergic to the ingestion of wheat, the original symptoms were reproduced by the acetylcholine derivative, acetyl-beta methyl choline chloride (mecholyl). This chemical was then administered daily for 20 to 60 days in increasing dosage according to the tolerance of the individual during a controlled symptom-free period. When wheat was readded to the diet of these people, the original symptom did not recur and they have remained well or greatly improved under observation for one year or longer. In four cases previous attempts to desensitize with wheat extract had been unsuccessful and in two, previous treatment with repeated injections of histamine had not influenced the course of the illness.

## CASE REPORTS

*Case 1.* W. A., a 23-year-old nurse. When first seen on July 5, 1937, she complained of nasal congestion and blocking, sneezing, severe cough with wheezing; all symptoms were of three years' duration. Examination revealed pale, boggy swelling of the nasal mucous membrane and wheezing râles in the chest. Nasal secretion and sputum contained chiefly eosinophile cells. Intradermal skin tests for common offending substances were entirely negative. The symptoms subsided on a milk, egg and wheat free diet and did not recur when milk and egg were readded to the diet. When wheat was added all original symptoms returned within 48 hours and promptly

\* Delivered before the Central Society for Clinical Research, Chicago, November 6, 1938. Mecholyl for this work was supplied through the courtesy of the Merck Laboratories, Rahway, N. J.

subsided when wheat again was withdrawn. Symptoms recurred occasionally during the next seven months due to her inability to follow a wheatless diet. Meanwhile an attempt was made to cause her to gain tolerance for wheat by adding it to the diet in small increasing quantities. On April 9, 1938, 8 milligrams of mecholyl were given by injection. This caused flushing, lacrymation, salivation, blocking of the nose, cough, chokiness and wheezing. These symptoms could be stopped within 30 seconds by applying a tourniquet above the site of injection and would recur within 15 seconds after the tourniquet was released. Symptoms persisted for about 20 minutes. On April 10 daily injections of mecholyl were started beginning with 0.5 milligram and increasing 0.5 milligram daily as tolerated. On April 30, 8 milligrams were again given and the general reaction was distinctly less than that caused by the original dose. Wheat was resumed in the diet on May 15 without recurrence of symptoms. Since that time she has continued to eat wheat and occasionally experiences some wheezing, but she can abort the symptom by an injection of mecholyl. She continued giving herself 5 milligrams of mecholyl weekly for two months. During the past year she has eaten everything and remained symptom-free.

*Case 2.* E. E. W., a 24-year-old man, a bookkeeper. When first seen January 25, 1938, he complained of spontaneous swellings of the hands, tongue, face, and feet, of three years' duration. On examination he appeared in excellent health. Laboratory findings were not significant. Intradermal skin tests were all negative except that a definite latent positive test with wheat extract was obtained. There was a wide zone of itching erythema present after 24 hours. The swellings subsided within 48 hours after wheat had been stopped in the diet. Swellings recurred when wheat was added to the diet for trial. Injections with wheat extract in increasing quantity were given from February 14 until April 12. Very small quantities of wheat were then started by mouth. Swellings recurred on April 22 when he was eating only one small saltine cracker daily. Daily histamine injections were given from April 10 to May 5. Small quantity of wheat again caused swellings to appear. On May 17, 1938, he was given 10 milligrams mecholyl which caused flushing, salivation, etc., and appearance of swelling on one arm. On May 18 injections of mecholyl were started with 0.5 milligram and increased 0.5 milligram daily. Five milligrams were all he could tolerate without discomfort and this dose was continued for one month. Occasionally swellings would appear soon after an injection, otherwise he was well. Wheat was resumed July 15. Swellings did not recur. On August 10, 1938, a few swellings recurred and mecholyl injections were resumed and were continued twice weekly (five milligrams). He had one attack of spontaneous edema in July 1939. Mecholyl (5 mg.) was again given for one month. Since that time his swellings have been negligible although he eats wheat regularly.

*Case 3.* F. S., a 25-year-old merchant's wife. Complaints at time of original examination on December 11, 1936, were attacks of sudden swelling of face, feet, hands and elsewhere, attacks of sneezing and nasal blocking, severe attacks of cough with wheezing and attacks of vomiting of six months' duration. Examination revealed swollen, pale, boggy, nasal mucous membrane, angioneurotic type swelling of face, wheezing râles on forced expiration. Laboratory work revealed nothing significant except eosinophile cells in the nasal secretion. Intradermal skin tests for common allergens were all negative except the wheat test which caused a latent reaction, an erythematous area, three cubic centimeters in diameter which persisted for several days. Symptoms subsided promptly upon withdrawal of wheat. A series of injections with wheat extract were given in 1937 followed by readdition of wheat to diet in infinitesimal quantity. After one full slice of bread was reached she began having nasal congestion and cough. Swelling of the face recurred at intervals, due to inability to avoid wheat entirely during 1937, and became quite severe in April, 1938. A strict wheat free diet was resumed. An injection of 5 milligrams of mecholyl was given on April 23 which produced, within a few minutes, sneezing, cough and wheez-

ing. Mecholyl was then given daily beginning with 0.5 milligram and increased 0.5 milligram with each subsequent injection. On May 15, 1938, 5 milligrams of mecholyl caused some salivation and tightness in the chest but not as much reaction as previously. Wheat was resumed in the diet as desired on May 20, and to date symptoms have not recurred.

*Case 4.* E. C., a 51-year-old farmer's wife. Her complaints on March 4, 1938 were the occasional recurrence of an eczematous rash on her arm for many years, a continuous eczematous facial rash of two years' duration and periodic swellings of the face for five months. On examination the eczema was found to be chiefly of flexural distribution with overflow on the thighs and on the ears. Laboratory work revealed no significant findings except blood eosinophilia. An intradermal skin test with wheat extract gave a latent positive test. Other tests for common allergens were negative. The swellings did not recur and the rash promptly subsided when wheat was eliminated from the diet. On March 18 wheat was added to diet. Two days later the rash reappeared and wheat was again stopped. She was given injections with wheat extract in increasing dosage from March 21 to April 15 when the injections were found to cause a flare-up of the eczema. On April 30 she was given 10 milligrams mecholyl which caused swelling of the face and next morning the rash was present in old areas on the arms. This course of events was repeated on May 6 and 7 thereby proving that eczema could be induced by mecholyl. On May 10, 0.5 milligram mecholyl was given and the dosage was increased 0.5 milligram daily if tolerated. On June 17, 10 milligrams mecholyl were given without causing swellings or recurrence of eczema. Wheat was again eaten on June 20 without causing any disturbance. Mecholyl was given weekly until August 1, 1938. There has been no recurrence of the original trouble to date although she eats some wheat daily.

*Case 5.* E. F., a 35-year-old woman, a stenographer. When first seen, on August 5, 1937, she complained of daily recurrences, for three years, of swollen areas which itched. Examination revealed nothing significant except large urticarial wheals and small erythematous areas. Laboratory work revealed nothing significant. Intradermal skin test with wheat extract gave a latent reaction about the size of a silver dollar within 24 hours. Other tests were negative. The swellings subsided entirely upon the withdrawal of wheat. A series of wheat injections was given and several attempts to add wheat in small increasing dosage resulted in recurrence of hives. On February 2, 1938, histamine injections were started and increased daily until 0.5 milligram was reached. The swellings continued to recur when wheat was eaten. On April 11, 8 milligrams mecholyl were given and produced much flushing, sweating, salivation and a few wheals. Mecholyl injections were given daily beginning with 0.5 milligram and increasing 0.5 milligram daily as tolerated. The usual dose was 3 milligrams. Wheat was readded to diet on May 24 without reproducing wheals. Since that time bread has been eaten as desired. Occasionally she has a few hives but these can be controlled by taking one or two injections of mecholyl weekly.

*Case 6.* R. S., an eight-year-old feeble minded boy of indigent family. Complaints when first seen, November 23, 1937, were asthma and nasal blocking of three years' duration. The asthma has been continuous throughout the year with aggravation by "colds" in winter. He was in St. John's Hospital from November 15, 1937 until January 15, 1938, during which time he was found to have allergic asthma and bronchial infection. Intradermal skin test for wheat was immediately positive with wheal formation. After subsidence of infection and elimination of wheat his symptoms stopped. Asthma recurred on February 9 when wheat was added to diet. Symptoms subsided within two days after withdrawal of wheat. Occasional flare-ups recurred in March and April when wheat was eaten. On April 12, 1938, he was given 5 milligrams mecholyl which caused much salivation and severe bronchospasm. Mecholyl was given regularly beginning with 0.5 milligram and increased 0.5 milligram every other day. After 5 milligrams were reached this dose was continued and

usually caused some wheezing. On June 15, 1938 wheat was again added to the diet but asthma did not recur. Weekly injections of mecholyl (5 mg.) were continued for two months. He had had no recurrence of asthma when last seen in August 1939.

*Case 7.* E. W., a 25-year-old school teacher. Her complaints on May 21, 1937, were perennial attacks of headache, vomiting, and asthma, with severe exacerbation in the autumn, of seven years' duration. Examination revealed nothing significant except wheezing râles at every examination. Intradermal skin tests were strongly positive to ragweed and to wheat. After the pollen season had passed it was found by repeated trial that she could remain free from asthma by elimination of wheat from her diet and that when this food was added some wheezing would recur. On April 9, 1938, she was given 8 milligrams of mecholyl and developed marked flushing, salivation, and severe bronchospasm. Daily injections of mecholyl were started on April 10 with 0.5 milligram and increased 0.5 milligram daily if tolerated. Regular dosage of about 3 milligrams was all that she could take without wheezing. After June 4 injections were given weekly until August 1. There was some recurrence of asthma during the ragweed season but only about 25 per cent as severe as that experienced in previous years. Preceding the ragweed season in 1939 mecholyl was given along with desensitizing injections of ragweed pollen extract and almost 100 per cent relief was obtained.

### DISCUSSION

The terms cholinergia and adrenergia are now in general use signifying imbalance of autonomic nerve activity. Patients who have a tendency to develop asthma, eczema, vasomotor rhinitis, urticaria and angioneurotic edema often demonstrate other features of cholinergia such as excessive sweating, salivation, indigestion of hyperacidity type, spastic bowel and dermographism. The cholinergic state in itself seldom causes distress; it is for the superficial symptoms that relief is sought. Adrenergic stimulants usually produce prompt but temporary relief from this group of cholinergic symptoms. Therapeutic measures should be directed against excessive action of acetylcholine itself. If choline esterase, the enzyme which normally causes immediate destruction of acetylcholine in the tissues, could be prepared and administered in a manner to diminish acetylcholine action it might be of some value. If the action of the choline esterase normally present could be made more effective a farther step in the right direction would be accomplished. By daily cholinergic stimulation with mecholyl we may be stimulating more efficient esterase action. Some degree of tolerance for cholinergic stimulation is, certainly, gained in some manner.

The question naturally arises concerning the interrelationship of acetylcholine and histamine. Histamine is probably released in the body tissues as a result of trauma, whereas acetylcholine is a normal physiologic stimulant. Acetylcholine is thought to act on arterioles causing their dilatation and histamine action is on the capillaries, probably making their walls more permeable. If histamine is injected in large dosage or is produced in hypersensitive individuals by trauma an anaphylactoid reaction results which probably disturbs the acetylcholine-choline esterase balance in certain shock organs. It is also probable that excessive acetylcholine action causes the liberation of histamine. Much work will be necessary to enlighten this problem.

Mecholyl has been used in a wide variety of allergic and exudative disorders in order to determine its limitations. It has been found to be most effective in aborting cases of angioneurotic edema, urticaria, and asthma in which the specific exciting factor could be determined and eliminated during the period when treatment with mecholyl was started. Mecholyl, if given repeatedly, usually causes allergies which are of continuous nature to become worse. I have not found mecholyl to be of value in the treatment of contact dermatitis and it is of doubtful value in cases of inhalant allergy.

The effects of this acetylcholine derivative when given in the manner we have described is probably superficial and although the status quo is altered there is little change in the basic hypersensitive or cholinergic states. Fundamental alterations in the method of living, working, eating and thinking may be necessary to enable the autonomic nervous system to readjust itself.





# THE CLINICAL APPLICATION OF THE DETERMINATION OF CIRCULATION TIME\*

By SAMUEL BAER, M.D., *Philadelphia, Pennsylvania*

THE estimation of the circulatory status of a patient is one of the most important problems the physician is called upon to face. Dyspnea, basal râles, tachycardia, hepatomegaly and peripheral edema usually indicate the presence of cardiac failure. But one may at times be sorely perplexed in determining whether the dyspnea complained of is cardiac, pulmonary or extrathoracic in origin; or whether the obvious pleural effusion is due to heart disease, thoracic tumor, malnutrition or hypertension.

Two of the factors influencing the maintenance of circulatory efficiency are the minute output of the heart, and the velocity of blood flow. The estimation of the cardiac output is still a rather technical and complicated procedure. But beginning with the work of Blumgart and his associates<sup>1</sup> in 1927, increasing interest has been paid to the study of the velocity of blood flow. The determination of the velocity of blood flow involves measuring the time required for the passage of a foreign substance from its point of introduction in the blood stream, until its arrival at another part of the body.

In a recent article, we<sup>2</sup> have discussed the progress made during the past decade in simplifying this test of cardiac function. What was once a highly complicated laboratory study, demanding expensive equipment and technical skill, is today a very simple procedure. So much have the methods for determining circulation times been improved, that they can be done inexpensively and with ease at the bedside or in the office. We propose in this paper to present again the technic adopted for determining circulation times, and cite a few examples of their wide clinical application.

## METHOD

With the patient in a recumbent posture, the calcium gluconate arm-to-tongue time is determined. A slight modification of the method originally described by Goldberg<sup>3</sup> is used. With the arm at the level of the right auricle an 18 gauge needle attached to a syringe containing 10 c.c. of 20 per cent calcium gluconate,† is inserted into an antecubital vein. Four cubic centimeters of this solution are then rapidly injected, the "end point" being a sensation of heat in the back of the throat and tongue. The wave of heat then spreads to the face, abdomen, perineum and extremities. The injection is timed by a stopwatch, from the instant it is begun until the moment the sensation of heat is felt in the throat. A duplicate reading is made within

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From the Wards and Outpatient Departments of Jewish Hospital, Philadelphia.

† Neo-Calglucon, supplied by Sandoz Chemical Works, Inc.

two or three minutes. With the same needle in situ or by another venipuncture, the ether arm-to-lung time is determined. This test, originally described by Hitzig,<sup>4</sup> consists of the intravenous injection of a mixture of five minims of ether and five minims of saline; the "end point" is the perception of ether vapor in the upper respiratory passages. Almost invariably the patient will cough, grimace or denote by sour facial expression the presence of the ether. Again, the injection is timed from the beginning to the moment the "end point" is recognized.

### THE NORMAL CIRCULATION TIME

The range of normal circulation times given by different observers has varied according to the methods used. But in the last few years, with improvement in the technic and refinement of the agents used, the results obtained have shown a surprising uniformity.

The ether time is a measurement of the time necessary for the ether to pass from the antecubital vein through the superior vena cava and right heart to the pulmonary artery and lungs. Ether is so readily diffusible that the time required to reach the upper air passages is negligible. The ether arm-to-lung time is therefore an index of the functional activity of the right heart. We<sup>2</sup> have corroborated the results of Hitzig<sup>4</sup> and others, who showed the normal arm-to-lung time ranged from 3 to 8 seconds.

Various substances have been suggested for determining the arm-to-tongue time. Decholin,<sup>5</sup> saccharin<sup>2, 6</sup> and more recently, calcium gluconate<sup>2, 3</sup> and magnesium sulphate<sup>7</sup> have been used. Irrespective of the agent, the arm-to-tongue time is that required for the injected material to pass from the antecubital vein through the right heart, the lungs, the left heart, the aorta and its branches, to the tongue. The velocity of blood flow from aorta to tongue is very rapid, so that the difference between the ether arm-to-lung time and the arm-to-tongue time is an accurate measure of left heart circulation. The determination of the left heart time is one of the best methods available for estimating the velocity of pulmonary blood flow. Normal arm-to-tongue times have been found to range from 8 to 16 seconds, irrespective of the method used. We agree with Goldberg that the calcium gluconate method is the most desirable to date for determining the arm-to-tongue time.

In tables 1 and 2 are listed the values obtained in patients by the ether and calcium gluconate methods.

### THE CIRCULATION TIMES IN VARIOUS ABNORMAL STATES

*Cardiac Disease.* Perhaps the widest application of these procedures is in the diagnosis of cardiac disease. With the development of cardiac failure, the circulation time becomes prolonged. Since the introduction of the ether arm-to-lung test by Hitzig, a number of papers<sup>8</sup> have appeared confirming the value of this test in the diagnosis of right heart failure. This

TABLE I

	Cases	Circulation Times—Ether	
		Range (Sec.)	Average (Sec.)
Normal	169	3.0-9.0	5.8
Pulmonary Disease	24	4.0-9.0*	6.1
Cardiac Disease	32	4.0-9.0	6.3
Without Failure	44	7.0-19.0	10.2
With Failure			

\* One patient with chronic fibroid phthisis had an ether time of 10.0 seconds.

TABLE II

	Cases	Circulation Times—Calcium Gluconate	
		Range (Sec.)	Average (Sec.)
Normal	133	8.0-16.5	12.3
Pulmonary Disease	35	8.0-16.0*	11.5
Cardiac Disease	36	8.5-17.0	13.1
Without Failure	46	16.0-55.0	24.6
With Failure			

\* One patient with unilateral functioning lung had a time of 7.5 seconds.  
One patient with chronic bronchial asthma had a time of 20.0 seconds.

procedure is safe, accurate, and easily carried out. With rare exceptions, an ether time within the range of normal is evidence against the presence of right heart failure. In right heart failure of course, this time is prolonged. In addition, the comparison of the ether and calcium gluconate times is of value in localizing the part of the circulation in which blood flow is retarded.

Of even greater value in the diagnosis of cardiac failure, is the estimation of the arm-to-tongue time. The fact that the normal circulation time with decholin,<sup>5</sup> saccharin<sup>2, 6</sup> and calcium gluconate<sup>2, 3</sup> averaged 12 to 13 seconds with all three methods, attests to the accuracy of the test. Since the circulation time is usually prolonged beyond 16 seconds in cardiac failure, the application of this test to the differential diagnosis of cardiac disease becomes apparent.

Blumgart and Weiss<sup>1</sup> stated that prolongation of the circulation times almost invariably indicated the presence of congestive heart failure. Tarr, Oppenheimer and Sager<sup>5</sup> found that in patients with congestive heart failure, the velocity of blood flow averaged 26 seconds, approximately double the normal average. Our work<sup>2, 9</sup> has added confirmatory evidence to these findings.

Circulation times in heart disease are shown in tables 1 and 2. Below are cited a few cases indicating the use of the tests in the diagnosis of heart disease.

#### CASE REPORTS

*Case 1.* Mrs. I. M., aged 22, was admitted to the maternity ward showing marked dyspnea, moist râles at both bases, a double mitral murmur, regular tachycardia of 120, enlargement of the left border of the heart to the anterior axillary line, and obvious peripheral edema. There was a history of a number of attacks of rheumatic fever. The diagnosis of cardiac decompensation complicating pregnancy was made. However, in view of the presence of polyhydramnios and a twin pregnancy, the cardiac consultant felt that the dyspnea, râles and edema were mechanical rather than cardiac in origin. He therefore advised against a Caesarean section. Circulation times were done, and an ether time of 5.2 seconds with a calcium gluconate time of 14 seconds obtained. These circulation times were confirmatory of the absence of cardiac failure. The patient went into labor, easily delivered of twins spontaneously, and was well from then on. Repeated circulation times were normal.

*Case 2.* Mrs. C. H., aged 48, was admitted on a number of occasions, for recurrent attacks of edema of the legs, dyspnea, palpitation, precordial discomfort and abdominal enlargement. Examination revealed a moderate hypertension, bilateral massive pleural effusion, ascites, and anasarca. Laboratory studies led to a diagnosis of chronic diffuse glomerulonephritis, though some of the staff felt the case was one of true lipid nephrosis. In view of the extreme dyspnea and anasarca, the possibility of cardiac failure was entertained. Circulation times, despite the extreme dyspnea and hydrothorax, were perfectly normal. (Ether time—5 seconds; calcium gluconate time—11 seconds.) Necropsy later revealed a chronic lipid nephrosis.

*Case 3.* Mr. B. G., aged 51, was admitted with a history of severe precordial pain, tachycardia and cyanosis. There was no evidence of pulmonary congestion or cardiac failure. A clinical diagnosis of acute myocardial infarction was made and an electrocardiogram revealed in addition, an auricular flutter. Circulation times were performed within 48 hours of admission, and indicated a normal ether time, but a saccharin arm-to-tongue time of 24 seconds. This suggested the existence of cardiac failure, which, however, was not apparent by physical examination. The following day obvious cardiac decompensation was found, with pleural effusion, râles, and cyanosis. Circulation times done one month later were completely normal, and the clinical evidence of failure had disappeared.

The test is of further value in observing the response of patients with obvious cardiac failure to therapy.

*Case 4.* Mrs. G. S., aged 48, was admitted on a number of occasions, with recurrent attacks of cardiac failure. Studies indicated the presence of rheumatic heart disease, with auricular fibrillation, aortic stenosis, mitral stenosis and regurgitation, and chronic cardiac failure. Three days after her admission in October 1936, an ether time of 19 seconds and a saccharin time of 26 seconds were obtained, indicating severe right heart failure.

Following digitalization, bed rest and diuretics, the ether time in 12 days was reduced to 10 seconds and the saccharin and calcium gluconate times to 20 seconds.

Stewart and Heuer<sup>10</sup> have recently studied the cardiodynamics of adhesive pericarditis. Following pericardiectomy, prolonged circulation times (determined by the decholin method) returned to normal or almost normal limits, *pari passu* with the clinical and laboratory evidence of improvement.

*Pulmonary Disease.* A number of observers<sup>11</sup> have shown the value of determining the circulation time in the differential diagnosis of pulmonary disease. Circulation times are almost always normal in uncomplicated pulmonary disease. The use of these tests in the differential consideration of pulmonary and cardiac disease is obvious. We have repeatedly found normal ether and calcium gluconate times (despite the presence of dyspnea and cyanosis) in carcinoma of the lung, chronic fibroid phthisis, bronchial asthma, emphysema, lung abscess, empyema and pneumonia. In a number of our cases of bronchial asthma, calcium gluconate circulation times have not only been normal, but were in the low range of normal 8 to 9 seconds.<sup>2</sup> Charr and Savacool<sup>12</sup> have recently shown that the development of cardiac failure in cases of chronic pneumoconiosis is accompanied by the prolongation of the circulation times.

*Disturbance in Metabolism.* Reports have been published concerning changes in the velocity of blood flow in metabolic disorders.<sup>13</sup> It has been fairly well agreed that with hyperthyroidism there is an increase in the velocity of blood flow and a more rapid circulation time, whereas in myxedema, the arm-to-tongue circulation time is prolonged. For the past year or so, we<sup>14</sup> have been attempting to correlate the arm-to-tongue circulation time with the basal metabolism rate, but have not completely analyzed our data as yet. Our studies thus far do not indicate the clear cut correlation between circulation times and basal metabolism rates shown by previous observers.

As a rule however, hyperthyroidism is associated with a rapid circulation time, and myxedema with a delayed time. Tarr, et al.<sup>5</sup> have suggested that a normal circulation time in the presence of obvious cardiac failure should make one look for factors tending to increase the velocity of blood flow. A case in point can be cited.

*Case 4.* Mrs. M. S., aged 46, was admitted in extreme dyspnea, with edema of the legs up to the knees. The patient had had a diffuse toxic goiter removed 8 years previously. Examination revealed no thyroid enlargement, marked dyspnea, some cyanosis, hypertension, cardiac enlargement with rapid regular tachycardia, bilateral pleural effusion and edema of the legs. The diagnosis of hypertensive cardiovascular disease with cardiac failure was made, but the question of thyrocardiac disease was raised. A basal metabolic rate determination would, we felt, be too inaccurate. Four separate circulation times with calcium gluconate averaged 8 seconds, despite the obvious cardiac failure. A diagnosis of hyperthyroidism was made, the patient was placed on Lugol's solution and digitalis, and a thyroidectomy then performed. After a somewhat stormy course, she recovered and was discharged in excellent condition. Interestingly enough, her circulation time on discharge was 12 seconds, though her cardiac failure was gone.

#### COMMENT

The cases cited illustrate perhaps the more important applications of the determinations of circulation times. But with the awakening of interest in this procedure in the past few years, a number of other uses have been found.

The circulation time is rapid in anemia, and prolonged in polycythemia

vera.<sup>15</sup> Webb, Sheinfeld and Cohn<sup>16</sup> have studied the circulation time in surgical cases. They stated that patients with prolonged circulation times were poorer surgical risks and had higher operative mortalities. At this hospital, studies are being made of the effect of pregnancy, of spinal anesthesia and operative procedures, and of peripheral vascular disease, on the circulation times. It must be remembered that the circulation time test is only a measure of the velocity of blood flow; it cannot tell us how much work the heart can do. But as an aid in determining the circulatory status of a patient, or in the differential diagnosis of a number of conditions, it is quite a valuable procedure.

### SUMMARY

1. The technic of determining circulation times with ether and calcium gluconate is discussed.
2. In 169 normal patients, the ether arm-to-lung time ranged from 3 to 9 seconds, averaging 5.8 seconds.
3. The ether time is prolonged in many cases of cardiac failure. A normal ether time is against the presence of right heart failure.
4. In 133 normal patients, the calcium gluconate arm-to-tongue time ranged from 8 to 16.5 seconds, averaging 12.3 seconds.
5. The calcium gluconate time is prolonged in cardiac failure.
6. Circulation times in uncomplicated pulmonary disease usually fall within normal limits.
7. The value of circulation times in the diagnosis of cardiac failure, and in the differentiation of various clinical conditions is discussed.

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## CARDIAC HYPERTROPHY; FORTY-TWO HEARTS WEIGHING 750 GRAMS OR MORE \*

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VERY large hearts are noted occasionally in any autopsy series, and formerly were usually ascribed to the effect of one of the infectious types of heart disease. During 1937 and 1938 there were 1372 autopsies performed at the Vancouver General Hospital, and among these were found 42 instances of hearts weighing 750 grams or more. Analysis of this group shows that the infectious type of heart disease is less commonly the cause of hypertrophy of this extent than are degenerative changes. Since it was our intention to study only the so-called "cor bovinum" we arbitrarily chose a weight approximately twice the upper limit of normal heart size. In this connection it is interesting to note that our ideas regarding normal heart weight have undergone revision upward in the last 20 years. It was formerly thought that the upper limit of normal heart weight was 300 grams for men and 250 grams for women. Aschoff<sup>1</sup> showed that in men a normal heart might weigh up to 355 grams, and Parkinson,<sup>2</sup> in the Lumleian Lectures in 1936, quoted Dr. William Evans who gave as the upper limit of normal 12 oz. (360 grams) for women and 13 oz. (390 grams) for men. Smith<sup>3</sup> has shown that the size of the heart bears a constant relationship to the body weight, the ratio for males being 0.43 per cent and for females 0.40 per cent. These figures, he considers, are accurate for body weights between 100 and 210 pounds, with an error of only 8 to 10 per cent. The weight of the heart in a 200 pound man is by this method found to be 390 grams. Unless this fact is kept in mind we are apt to draw false conclusions from earlier analyses<sup>4</sup> where hearts weighing even less than 300 grams were described as hypertrophied. White<sup>5</sup> gives the normal as 0.40 to 0.45 per cent, with a range of from 0.35 to 0.50 per cent. Figures over 0.50 per cent can be safely regarded as showing hypertrophy.

The incidence of cardiac hypertrophy of the extent described in these cases is not easy to ascertain. Ophüls,<sup>6</sup> in a careful analysis of 3000 autopsies, mentions cardiac hypertrophy in association with arteriosclerosis in 10 per cent. Another 10 per cent showed endocarditis, and some of these would undoubtedly have shown hypertrophy. Further instances of hypertrophy occurred among cases of nephritis. The extent of the hypertrophy was not mentioned. Brines,<sup>7</sup> in an analysis of 1535 autopsies, found heart disease in 20 per cent and kidney disease in 14 per cent. Cardiac hypertrophy was mentioned only in the group showing coronary sclerosis, where it occurs in 50 per cent of the 46 cases. Grant,<sup>8</sup> in a follow-up study of 1000

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cases of heart disease over a ten-year period, noted 142 autopsies in the 470 deaths. Among these autopsies the heart weight was recorded in only 87 instances and in 26, or 29 per cent of these, the heart weight was more than 700 grams. If we apply Brines' <sup>7</sup> figures to our entire autopsy series we should have expected to find 274 cases of heart disease and 192 cases of kidney disease. The 42 instances of gross cardiac hypertrophy would, therefore, equal 9 per cent of the 466 cardiorenal cases, and 3 per cent of the entire series of 1372 cases. Boyd,<sup>9</sup> in an analysis of over 950 autopsies at the Toronto General Hospital in the years 1937 and 1938, found 85 cases showing cardiac hypertrophy. Of these only two were of 750 or more grams, and 10 of 650 grams or more in weight. Just why the incidence of extreme cardiac hypertrophy should be so much greater in Vancouver than in Toronto is not clear. It represents another instance in the peculiar geographical variation in pathological processes. The West is still a pioneer country, and the character of much of its industry is more strenuous than that of the East.

TABLE I  
Report on Autopsies, 1937, Vancouver General Hospital

	Hospital Deaths						Total	Out- side Cases	Total Au- topsies
	Patients			Stillbirths					
	Priv.	Staff	Total	Priv.	Staff	Total			
Deaths	448	600	1108	34	14	48	1156	37	638
Referred to coroner	58	25	83				83		
Available for autopsy by hosp. pathologist	390	635	1025	34	14	48	1073		
Autopsies done by hosp. pathologist	116	473	589	3	9	12	601		
Percentage	29.7	74.5	57.4	9	64	25	56		
1938									
Deaths	449	679	1128	32	10	42	1170	65	734
Referred to coroner	49	29	78						
Available for autopsy by hosp. pathologist	400	650	1050	32	10	42	1092		
Autopsies done by hosp. pathologist	141	509	650	12	7	19	669		
Percentage	35.2	76.8	62	37.5	70	45.2	61.3		1372

Table 1 shows a statistical summary of the deaths and autopsies at the Vancouver General Hospital during the years 1937 and 1938. It should be pointed out that an autopsy rate of 62 per cent of all deaths and 76 per cent for the charity patients represents an excellent showing in a large, general, non-teaching hospital.

In tables 2 to 5 there is a tabulation of the 42 cases, showing age, sex, heart weight and postmortem diagnosis arranged under the following four headings: rheumatic heart disease, luetic heart disease, arteriosclerotic heart disease, and nephritis. There were no instances in this series of acute or subacute endocarditis or of thyroid heart disease. The division into the four main headings was made on a clinical and on a pathological basis. The distinction between arteriosclerotic heart disease and nephritis was not always clear cut. The latter classification was used when the kidney lesion was considered the primary cause of death, and usually meant a chronic glomerulonephritis with or without nephrosclerosis. In many of those listed as arteriosclerotic heart disease there was a degree of nephrosclerosis sufficient to account for some of the hypertension and accompanying cardiac hypertrophy, but the heart disease was considered primary. In the rheumatic and luetic cases the differentiation was less difficult though even in these cases there were instances of overlapping, in which more than one type of heart disease was present. Undoubtedly there were among these cases instances of malignant hypertension which came to their deaths as a result of cardiac or cardiorenal damage.

TABLE II  
Rheumatic Heart Disease—8

Serial No.	Age Sex	Ht. Wt.	Postmortem Diagnosis
1	53M	890	Aortic and mitral stenosis.
9	50M	800	Aortic stenosis.
20	47F	1000	Adhesive pericarditis; chronic nephritis; (H).
21	28M	1000	Aortic regurgitation; mitral regurgitation; chronic pericarditis; (H).
23	48F	780	Mitral stenosis (H); coronary sclerosis; old infarct; cerebral infarcts.
30	42M	1000	Aortic stenosis.
32	53M	780	Aortic stenosis.
36	11M	800	Chronic myocarditis; no valvular disease; pericardial adhesions.
	Av.	881	(H) indicates a significant hypertension.

TABLE III  
Luetic Heart Disease—7

Serial No.	Age Sex	Ht. Wt.	Postmortem Diagnosis
2	62M	1000	Aortitis with regurgitation; coronary sclerosis.
3	42M	1750	Aortitis with regurgitation; subacute nephritis.
22	48F	840	Aortitis with regurgitation; (H); coronary orifices narrowed.
25	38M	950	Aortitis with regurgitation; coronary orifices narrowed.
28	43M	1020	Aortitis with regurgitation; (H); narrowed coronary orifice.
33	39M	1040	Aortitis with regurgitation; coronary orifices narrowed.
38	43M	780	Aortitis with regurgitation; right coronary occluded.
	Av.	1054	(H) indicates a significant hypertension.

TABLE IV  
Arteriosclerotic Heart Disease—14

Serial No.	Age Sex	Ht. Wt.	Postmortem Diagnosis
4	57M	850	Coronary sclerosis; mitral sclerosis; nephrosclerosis; old hemiplegia.
6	64M	860	Aortic stenosis; (H); coronary sclerosis; old infarct.
7	51M	1090	Aortic stenosis; luetic aortitis.
10	58M	800	Coronary sclerosis; (H); old infarct; few pericardial adhesions.
11	87M	750	Coronary sclerosis; (H); few pericardial adhesions.
14	56M	760	Generalized arteriosclerosis; (H); coronary sclerosis; nephrosclerosis.
15	52M	750	Coronary sclerosis with thrombosis.
16	67M	750	Coronary thrombosis; (H); chronic nephritis.
18	56M	750	Coronary sclerosis with thrombosis.
27	45M	780	Coronary thrombosis; old infarct; (H); mitral and aortic sclerosis.
37	60M	750	Coronary sclerosis with thrombosis; old infarct.
40	44M	930	Generalized arteriosclerosis; (H); hydronephrosis.
41	64M	840	Coronary sclerosis with thrombosis; old infarct; terminating pericarditis.
42	67M	750	Coronary sclerosis with thrombosis; (H); luetic aortitis; aortic sclerosis; cerebral infarct.
	Av.	815	(H) indicates a significant hypertension.

TABLE V  
Nephritis—13

Serial No.	Age Sex	Ht. Wt.	Postmortem Diagnosis
5	68M	800	Chronic nephritis; and nephrosclerosis.
8	74M	770	Chronic nephritis; (H); coronary sclerosis.
12	74M	750	Chronic nephritis; (H); aortic sclerosis.
13	61M	810	Chronic nephritis; (H); chronic myocarditis.
17	68F	750	Chronic nephritis; luetic aortitis; no regurgitation.
19	88F	750	Chronic nephritis; (H); chronic myocarditis.
24	70M	900	Chronic nephritis; generalized arteriosclerosis.
26	68M	810	Chronic nephritis; coronary sclerosis; (H).
29	88M	780	Chronic nephritis; mitral and aortic sclerosis; coronary sclerosis.
31	57F	900	Chronic nephritis; (H); generalized arteriosclerosis.
34	73M	780	Chronic nephritis; (H); aortic sclerosis; coronary sclerosis.
35	75M	780	Chronic nephritis; (H); generalized arteriosclerosis.
39	54M	1050	Chronic nephritis with acute exacerbation; (H).
	Av.]	817	(H) indicates a significant hypertension.

The four types of heart disease show some difference in the average weight of these hypertrophied hearts:

Rheumatic.....	8 cases	881 grams
Luetic.....	7 "	1054 "
Arteriosclerotic.....	14 "	815 "
Nephritic.....	13 "	817 "

It would seem significant that the heart weight in the luetic group averaged about 200 grams more than in the other groups. One reason for this

may be that aortic lesions obviously add greatly to the work of the heart, especially the left ventricle, and in the main the coronary arteries are relatively free from sclerosis in this group. Thus, with tremendous increase in the demands on the heart muscle and in the presence of an adequate blood supply the greatest hypertrophy occurs. The narrowing of the orifices of one or both of the coronary arteries is probably a late development in the course of luetic aortitis.

Presented in tabular form the etiologic basis for the hypertrophy was as follows:

Rheumatic		
Chronic adhesive pericarditis.....	1	
Chronic myocarditis.....	1	
Valvular disease.....	6	
Aortic.....	5	
Mitral.....	1	8
Luetic		
Aortitis		
All with regurgitation.....	7	
Arteriosclerotic		
Aortic stenosis.....	2	
Coronary sclerosis.....	10	
With thrombosis.....	8	
Generalized arteriosclerosis and hypertension.....	2	14
Nephritis (hypertension).....		13
		<hr/> 42

These cases can be rearranged according to the structural or anatomic causes for the hypertrophy as follows:

Valvular defect.....	15		
Aortic			
Stenosis.....	R.4	A.2	6
Regurgitation.....	R.1	L.7	8
Mitral			
Stenosis (with hypertension).....			1
Pericarditis (with nephritis).....			1
Myocardial involvement.....			13
Rheumatic.....			1
Coronary sclerosis.....			10
Coronary thrombosis.....			8
Generalized arteriosclerosis and hypertension.....			2
Nephritis.....			13
			<hr/> 42

The earlier teaching<sup>4</sup> as to the cause of cardiac hypertrophy indicated that aortic stenosis and adhesive pericarditis were common. In this series there were only six instances of aortic stenosis and only one of adhesive pericarditis. In the latter case an accompanying chronic nephritis undoubtedly accounted for some part of the hypertrophy. These findings would confirm the present view that adhesive pericarditis is of itself rarely, if ever, a cause of hypertrophy, and where the combination is found the cardiac enlargement is due to some accompanying cardiac abnormalities.<sup>2</sup>

The distribution of these hearts according to weight (free of clot) was as follows:

Over 1000 grams.....	5
1750-1090-1050-1040-1020	
901-1000 grams	
1000-1000-1000-1000-950-930.....	6
801-900 grams.....	9
750-800 grams.....	22
	<hr/> 42

The largest heart in this series, 1750 grams, occurred in a case of luetic aortitis with free aortic regurgitation, a subacute nephritis and moderate hypertension. The patient died of a lobar pneumonia. There were nine hearts weighing 1000 grams or more. It is generally agreed that when the heart weight exceeds 0.5 per cent of the body weight hypertrophy is present. In this series accurate body weights were not available in every case. In 10 patients in whom body weight (free of edema) had been recorded, the heart weight percentage (table 6) showed a variation from 0.93 to 1.8 in the adults. The one child in this series showed a heart equal to 2.6 per cent of his body weight. Table 6 shows that most of the adult cases were twice the upper limit of normal heart size and that four were three times that amount.

TABLE VI  
Percentage Heart Weight of Body Weight

No.	Body Wt. Lbs.	Ht. Wt. Grams	%
36	67½	800	2.6
21	122	1000	1.8
25	139½	950	1.5
34	112	780	1.5
39	148	1050	1.5
23	145	780	1.2
37	135	750]	1.2
38	143	780]	1.1
42	180	750]	1.0
27	184	780]	0.93
<hr/>			
NORMAL.....		Men.....	0.43
		Women.....	0.40
HYPERTROPHY OVER.....			0.50

#### CLINICAL ANALYSIS

The age in this group varied from 11 to 88, with 28 of the 42 cases past 50 years of age.

The sex distribution is of some interest, as of the 42 cases 36 were men and 6 women. Since hypertension and rheumatic heart disease both contribute to this series, and both show a preponderance of females, the large percentage of males in our series is not easily understood. The proportion of males to females is similar to that found in the clinical groups of arteriosclerotic heart disease and luetic heart disease in our hospital.

In reviewing the clinical records we were impressed by the short history given by many of these patients. It was not unusual for them to give a history of only a few weeks' or even only a few days' duration of the symptoms of congestive heart failure, dyspnea, weakness, and dropsy. In a few instances the patient was brought into the hospital for other than cardiac symptoms, as, for example, case 34 was brought in with ruptured gastric ulcer and case 11 with a primary carcinoma of the lung. In spite of this short history we hold the belief that the hypertrophy observed was a long time, months or even years, in developing. In this connection it is interesting to note that hypertrophy can develop in a very short time. J. M., a man aged 22 (not included in this series), became ill with an acute febrile illness, with pain in chest and cough, on October 7. On October 14, when he first consulted his doctor, a roentgen-ray showed a heart of normal size. One week later, October 21, a roentgen-ray showed tremendous enlargement of the heart shadow, which was then considered to be due to cardiac dilatation accompanying the acute aortic endocarditis that had developed. He died on November 7, one month after the onset of the illness and three weeks after a roentgen-ray showing a normal heart shadow. At autopsy, which showed an acute aortic endocarditis, his heart was greatly hypertrophied, weighing 950 grams. The rate of hypertrophy must vary considerably and was probably more than usually rapid in this case because of the youth of the patient. Palmer<sup>10</sup> mentions an instance of rapid hypertrophy in a girl of 12 with nephritis and hypertension in which a considerable increase of the heart shadow occurred in six months.

Physical signs of congestive failure were the rule, and in 35 of the 42 cases some degree of chronic congestion was present. These signs were tabulated as: (1) congestion of the lung bases; (2) peripheral edema; (3) enlargement of the liver; and (4) abnormal distention of the neck veins. In nine cases all four were noted; in 22 some combination of two or more of the four was present; in four only basal pulmonary congestion was found; and in seven there were no such signs present.

The blood pressure was recorded in 41 cases. It was classified as elevated if recorded as over 160 systolic or over 100 diastolic. It was elevated in 23 cases, below normal in two, and within normal limits in 16. From indications secured from the history and other examinations, such as the eye-grounds, it is our opinion that many of these patients had shown an elevated blood pressure previously.

Clinical signs of cardiac enlargement were noted in 35 of the 38 cases in which some record of this finding was made. For the purposes of this tabulation the grade of enlargement was classified according to the location of the left border as follows:

1. At midclavicular line.....	13 cases
2. Outside midclavicular line.....	5 "
3. In anterior axillary line.....	10 "
4. In axilla.....	7 "

Seventeen of the patients showed hearts enlarged to grades 3 and 4. It was surprising that, in view of the tremendous hypertrophy present, the clinical evidence of enlargement should not have been even more obvious. Roentgen-ray examination of the heart was carried out in 19 instances and in all revealed great enlargement.

Urinalysis revealed the expected findings in congestive failure. No renal function studies were carried out in these patients except the estimation of non-protein nitrogen in the blood which was increased in the nephritic group. No significant information was secured from the blood counts or the sedimentation rates performed on these patients.

Blood Kahn tests, done in 27 cases, were positive in seven and negative in 20. In the remaining 15 no report was available. Of the seven showing a positive Kahn, five had aortitis with regurgitation as the primary cause of the cardiac hypertrophy, and the other two showed aortic stenosis and cor-

TABLE VII  
Analysis of Electrocardiograms

Case No.	Rhythm	Axis Dev.	R or S - T	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	B.P.	Coronary Arteries <sup>1</sup>	Type <sup>2</sup> H.D.
1	F	R	N	U	I	I	O	1	R
2	R	O	1 and 2 low	I	I	F	O	3	L
3	R	L	1 and 2 low	I	I	U	O	N	L
4	R	O	N	I	I	F	O	2	A
7	R	L	1 and 2 low	I	I	U	O	1	A
9	R	L	1 and 2 low	I	F	U	O	1	R
10	R	L	1 low	I	U	U	H	3	A
13	F	O	N	I	I	F	H	2	N
14	R	L	N	U	U	F	H	2	A
15	R	O	N	F	F	I	O	4	A
16	R	L	N	U <sup>3</sup>	U	U	H	4	A
17	R	L	1 low	I	U	U	O	N	N
20	R	L	1 and 2 low	I	I	U	H	2	R
21	R	L	1 and 2 low	I	I	U	H	N	R
22	R	L	1 low 3 high	I	I	U	H	N.O.	L
23	F	R	N	F	I	I	H	2	R
24	F	L	N	I	F	F	N	2	N
25	R	L	1 low	N	N	N	H	N.O.	L
27	R	L	1 low	I	I	U	H	4	A
28	R	B.B.	1 high 2 and 3 low	U	I	I	H	N.O.	L
29	H.B.	L	2 low	I	U	U	O	2	N
35	F	O	1 and 2 low	I	I	F	H	2	N
37	R	L	1 and 2 low	I	I	U	O	4	A
38	R	O	2 slurred	F	F	U	O	N.O.	L
40	R	L	1 and 2 low 3 high	I	U	U	H	2	A
42	R	L	1 and 2 low	I	I	U	H	4	A

1. Graded as follows:

1. Beading.
2. Sclerosis.
3. Stenosis.
4. Thrombosis.
- N.O.—Narrowed orifice.

2. R—Rheumatic.

- L—Luetic.  
A—Arteriosclerotic.  
N—Nephritic.

onary sclerosis respectively as the primary cause, with an aortitis as an accompanying finding. Among those with negative Kahn tests there were two with luetic aortitis found at autopsy. One of these cases, number 25, a man aged 38, with no rheumatic history showed a Corrigan pulse, a blood pressure of 120 systolic and 20 diastolic to 160 systolic and 70 diastolic, and a systolic and diastolic murmur at the aortic area. His blood Kahn was negative on two occasions. The other case, number 17, a woman aged 68, was diagnosed as chronic myocardial degeneration and chronic nephritis, and at autopsy was found to have in addition a luetic aortitis. In one additional case, number 33, a clinical diagnosis and the pathological finding of luetic aortitis were noted, but no record of a blood Kahn was found.

Electrocardiograms were obtained in 26 of the 42 cases at intervals of a few days to several months before death. In none of these was a normal tracing found. The pertinent electrocardiographic findings are tabulated in table 7 along with the blood pressure, condition of the coronary arteries, and the postmortem diagnosis. The commonest form of tracing was one showing a left axis deviation with a depressed R-T segment in the first lead and an inverted  $T_1$  and  $T_2$  and upright  $T_3$ . The rhythm was usually regular. Only five of these cases showed an auricular fibrillation, and one a partial heart block. Left axis deviation was the rule, but in six cases there was no abnormal deviation; in two it was to the right; and in one a branch block was present. The R-T or S-T segment was usually abnormal, the level of this segment in the first or second lead being below the iso-electric line in 18 of the 26 cases. It was in T-wave changes that the most consistent deviation from the normal was noted. The changes found were classified as follows:

Normal.....	3 (In one case $T_1$ was definitely flattened).
$T_1$ upright $T_2$ and $T_3$ inverted.....	3
$T_1$ inv. $T_2$ and $T_3$ flat or upright.....	7
$T_1$ and $T_2$ inv. $T_3$ flat or upright.....	13

In 20 of the 26 cases, therefore, the T-wave was definitely abnormal and was of the type usually associated with the myocardial changes that result from deficient coronary blood flow, usually due to coronary sclerosis, but also due to narrowing of one or both coronary orifices by aortic valvular disease or aortitis. The blood pressure was normal in 12 and elevated in 14 of these cases, although as previously mentioned it is our impression that many had had a previous hypertension. The presence or absence of hypertension bore no relation to the electrocardiographic changes as listed, and this would seem to confirm the observation made by one of us (G. F. S.)<sup>11</sup> that cardiographic changes of this sort are due to coronary artery disease and the associated myocardial involvement rather than to hypertension per se.

The coronary arteries showed some evidence of abnormality in 23 of the 26 cases, i.e., a beading in three, a diffuse sclerosis in nine, a stenosis in two, a thrombosis in five, and narrowing of a coronary orifice in four. The normal coronary arteries were noted in one rheumatic, one nephritic, and one



luetic case, in each of which the cardiogram was abnormal, and in two of which the blood pressure was normal. The massive hypertrophy would of itself account for some of the electrocardiographic change.

### PATHOLOGICAL FINDINGS

The enlargement found was, in practically every case, a general hypertrophy and dilatation. The walls of both the left and right ventricle were greatly thickened. No evidence of enlargement of any one chamber, or of the inflow or outflow hypertrophy of Parkinson<sup>2</sup> was noted. This was not surprising inasmuch as these cases represented an extreme degree of cardiac enlargement past the stage of localized hypertrophy. Microscopically the heart fibers were enlarged. It was not true that the largest fibers were found in the largest heart, case 3, in which the heart weight was 1750 grams. The amount of myocardial degeneration and fibrosis showed considerable variation and raised the question as to the relative importance of true muscular hypertrophy and fibrosis as the cause for the increased heart weight. In most instances, of course, both enlargement of the individual muscle fibers and fibrosis were present. The weight as recorded was, of course, the weight of the heart alone free of blood and blood clot. In the tabulation tables 2 to 5 only the important cardiac postmortem findings are listed; and the rule was that most hearts showed overlapping, with two or more factors present to account for the hypertrophy.

The condition of the coronary arteries was carefully noted in every case, and in only seven of the 42 were they found to be normal. In these cases other obvious causes for hypertrophy were present. The coronary arteries in the remaining 35 cases were described as: beading or scattered plaques, 5; diffuse sclerosis, 13; stenosis, 4; thrombosis, 8; narrowed orifice (luetic aortitis), 5.

The liver showed chronic passive congestion in every case. In one instance, number 29, there was in addition a portal cirrhosis. The kidney findings have already been mentioned, the commonest lesion found being a chronic glomerulonephritis with an accompanying nephrosclerosis of varying degree in some cases.

There were in certain instances autopsy findings in addition to the cardio-renal damage sufficient to be a factor in causing death. Some of these have already been mentioned. They were a lobar pneumonia in number 3, bronchogenic carcinoma in number 11, enlarged prostate in number 24, cirrhosis of the liver, enlarged prostate and pulmonary abscess in number 29, perforated gastric ulcer in number 24, terminal hemorrhagic pancreatitis in number 35, hydronephrosis due to aberrant artery in number 40. In the remaining 35 cases the death was due solely to the cardio-renal-vascular changes.

The high incidence of coronary artery involvement in this series of enlarged hearts is in keeping with the observation of Palmer<sup>10</sup> that coronary

sclerosis per se is an important factor in the production of hypertrophy. He reports five cases with coronary sclerosis followed over one to four years, during all of which time the blood pressure remained normal, that showed progressive enlargement. Where, as is usual, the coronary sclerosis is associated with a hypertension the resulting hypertrophy is much greater. This relation of coronary sclerosis to the production of hypertrophy has some bearing on this present series. In the past the infectious types of heart disease, rheumatic or luetic, were considered the most likely causes of great enlargement. In recent years the importance of the degenerative changes associated with coronary sclerosis and hypertension has received more recognition. In this group it seems significant that only 15 of the 42 were due to the infectious type of heart disease, whereas 27 were due to degenerative changes. This present series may be affected to a certain extent by the fact that we have in this area, as has been reported for the Northwestern States,<sup>12</sup> a low incidence of rheumatic infection. In New England the incidence of rheumatic infection and, therefore, of the percentage incidence of rheumatic heart disease would be much greater.

### SUMMARY

Forty-two cases of cardiac hypertrophy of sufficient degree to be called true instances of *corda bovina* were collected from the autopsy material of the Vancouver General Hospital in 1937 and 1938.

These cases were all of approximately twice the upper limit of normal heart weight and they illustrate the importance of heart strain, work hypertrophy, in the production of cardiac enlargement.

Hypertension was probably the important clinical factor in producing this hypertrophy.

Chronic adhesive pericarditis was notable because of its infrequency.

Of the valvular lesions the aortic were commonest.

Coronary sclerosis was the important pathological finding and this combined with the hypertension produced the great enlargement.

The infectious types of heart disease accounted for only 15 cases, whereas the degenerative, arteriosclerotic changes accounted for 27.

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## FELTY'S SYNDROME; ITS SEVERAL FEATURES, INCLUDING TISSUE CHANGES, COMPARED WITH OTHER FORMS OF RHEU- MATOID ARTHRITIS \*

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IN 1924 Felty<sup>1</sup> described a syndrome occurring in five cases characterized by chronic rheumatoid arthritis, splenomegaly, and leukopenia. The syndrome occurred in individuals of middle age; all patients gave a history of marked loss of weight and all were undernourished; the arthritic process was distinctly chronic with an average duration of four and one-half years; the onset was either acute or gradual; and in the extremities occurred a generalized articular aching, which was mild but persistent, and accentuated by an occasional acute exacerbation.

In two of the cases the spleens were palpable just below the costal margins, in two others at the level of the umbilicus, and in the fifth case at a point five centimeters below the umbilicus. The spleens were firm, but not tender. No abnormality in the size or consistency of the livers was noted. In two cases the lymph glands were not enlarged, but in the other three the axillary, inguinal and epitrochlear nodes showed definite enlargement.

In four of the cases there was a slight secondary anemia, the red cells varying from 3.75 million to 4.80 million, and the hemoglobin from 70 per cent to 80 per cent. The color index averaged 0.85. Felty described a striking leukopenia, varying from 1000 to 4200 white blood cells, which he felt was a distinctive feature in every case. The differential formulae were not characteristic and eosinophilia was not present. The urines were normal with the exception of one case in which a urobilinuria was present. Stool examinations were negative. None of the patients showed any evidence of lues either serologically or on general examination. Three patients were afebrile during their hospital stay; two ran a low fever which subsided after one or two weeks.

In discussing this syndrome Felty advanced two likely explanations for it: (1) "The several features are manifestations of one pathological process, caused by a noxa which simultaneously affects the joints, the spleen, and the blood leukocytes. (2) The syndrome is merely the confusion of two separate clinical entities occurring coincidentally in the same individual. Taken separately without regard to the arthritis, the enlarged spleen with leukopenia and slight secondary anemia, the slight pigmentation of the skin, and the presence in the urine of urobilin, in the one case in which this was

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sought for, are typical features of early Banti's disease." Felty concludes by stating that "one is more or less forced to the conclusion that this syndrome is a distinct clinical entity of which the outstanding symptoms are those related to the joints and the outstanding signs are the enlarged spleen and the blood picture."

Since the original report by Felty,<sup>1</sup> Hanrahan and Miller (1932),<sup>2</sup> Singer (1933),<sup>3</sup> Alessandrini (1934),<sup>4</sup> Craven (1934),<sup>5</sup> Price and Schoenfeld (1934),<sup>6</sup> Fitz (1935),<sup>7</sup> Singer and Levy (1936),<sup>8</sup> Williams (1936),<sup>9</sup> Reich (1936)<sup>10</sup> have described other patients with a syndrome of rheumatoid arthritis, an enlarged spleen, adenopathy, pigmentation of the skin, secondary anemia and leukopenia. Some of these observers have considered such a syndrome a definite clinical entity. Others have believed the "Felty syndrome" to be an uncommon but not unexpected manifestation of chronic rheumatoid arthritis. Still others have looked upon the syndrome as an end result of long standing infection.

### PROBLEM

Rheumatoid arthritis has long been considered a disease resulting from a source of infection which does not have its primary location in the joint. Hench<sup>11, 21</sup> has repeatedly emphasized that although the joints may be the most evidently diseased structures in rheumatoid arthritis, the course of the disease, its systemic manifestations and the pathological changes found in other tissues clearly demonstrate that the disease is a generalized one. Furthermore, if rheumatoid arthritis is a generalized disease, in some cases at least it would be expected grossly to involve other tissues such as the skin, muscle, spleen, liver, lymph glands and bone marrow. Many cases have been reported showing several of these systemic abnormalities. Little attention has been focused on the skin, muscle and vascular changes associated with rheumatoid arthritis.

With the belief that a pathological study of the skin, muscles and small blood vessels removed from an area unrelated to an involved joint in patients with rheumatoid arthritis might give further evidence whether or not the disease process was a generalized one, and also might aid in determining whether Felty's syndrome was a clinical entity or just an expected complex of the disease, we obtained such an examination on a group of 11 arthritics at the University Hospital. Four cases making up Group I (numbers 1, 2, 3 and 4) presented the entire syndrome described by Felty, that is, rheumatoid arthritis, leukopenia, enlarged spleen, anemia, and adenopathy. Three patients had biopsies of the skin and muscle. The fourth had a lymph gland biopsy. Four cases making up Group II (numbers 5, 6, 7 and 8) were selected as a measure of control, since they presented, in addition to rheumatoid arthritis and an enlarged spleen, a leukocytosis instead of leukopenia. Four cases making up Group III (numbers 9, 10, 11 and 12) were selected since they presented rheumatoid arthritis without either a palpable spleen or a leukopenia.

A brief summary of these cases together with their biopsy findings is as follows:

### GROUP I

#### FELTY'S SYNDROME

##### *Rheumatoid Arthritis, with Leukopenia, Splenomegaly, Anemia and Adenopathy*

*Case 1.* A white male (B. R.), aged 67, was admitted to the University Hospital July 27, 1934, complaining of pain and stiffness in his joints of seven years' duration. Four to five months prior to admission the joint involvement had become worse with increasing stiffness and loss of motion. There had been a chronic cough for two to three years, productive of two to three tablespoonsful of yellow sputum daily. There had been a loss of 25 pounds of weight since 1933. His past history was unessential with the exception of a nocturia of one to three times which he had had for a number of years.

*Examination:* Showed a pale, undernourished, asthenic-appearing white adult male. There was fusiform swelling of the wrists and interphalangeal joints of the hands, with limitation of motion in the hands, wrists, elbows, shoulders and cervical spine. There were bean-sized lymph glands in the inguinal and epitrochlear regions. The lungs showed a few fine post-tussive râles at the right apex anteriorly below the clavicle. In the abdomen the liver border was palpable one finger's breadth below the costal margin on deep inspiration. The spleen was also "palpable." Otherwise the physical examination was not significant.

*Laboratory findings:* Several urine examinations were negative. The blood examination on admission showed a 55 per cent hemoglobin, 4,300,000 red blood cells, 2,850 white blood cells. The differential smear showed the polymorphonuclears to be 45 per cent, basophiles 1 per cent, eosinophiles 1 per cent, lymphocytes 45 per cent, mononuclears 8 per cent. The red blood cells showed moderate acromia with no change in their size or shape. Platelets were normal in number. Numerous subsequent blood examinations were made, and on iron therapy the hemoglobin rose from 52 per cent to 74 per cent at the time of discharge. There was also a gradual increase in the red blood cell count up to 5.2 million at the time of discharge. The white blood cells varied, ranging from 2,700 to 4,200. The routine stool examination was negative. Routine blood Kahn test was negative. Basal metabolic rate was —5 per cent. A biopsy of the calf muscles on August 9, 1934 showed a marked fibrosis of the corium (see figure 1). In the adipose tissue were small blood vessels which showed practically complete obliteration, as well as several with active inflammation. The muscle showed a localized increase in interstitial nuclei with small perivascular infiltrations (see figure 1 A). A roentgen-ray examination of the left shoulder, right wrist and hand showed osteoporosis and irregularity of the lateral and medial margins of the first phalanges of the right hand, probably due to arthritis. A stereoscopic projection of the thorax showed a minimal parenchymal lesion of the right apex evidently tuberculous in nature. The activity by roentgen-ray was indeterminate at that time. During the patient's hospitalization he had frequent elevations of temperature to 99.5° F. and above, and on one or two occasions to 101°. The pulse ranged from 70 to 108 per minute. All sputum examinations were negative for acid fast bacilli and it was concluded that the parenchymal lesion in his right apex was inactive. He was discharged on September 18, 1934.

He returned to the University Hospital on July 10, 1935, stating that his weakness, ease of fatigue and tiredness of the legs had increased, and that he had lost 10 more pounds in weight. A slight incontinence of urine had developed since his last admission.



FIGS. 1-1 A.

The examination was essentially the same as before except that the prostate gland was hard, showed a two plus enlargement, and was quite nodular. The Department of Urology made a diagnosis of carcinoma of the prostate. Roentgen-ray reports showed no activity of the chest lesion. There was no evidence of metastatic carcinoma of the spine or pelvis. A blood count on readmission showed the following findings: Hemoglobin 68 per cent, red blood cells 4,120,000; white blood cells 2,500; polymorphonuclears 42 per cent, eosinophiles 1 per cent, lymphocytes 47 per cent, mononuclears 5 per cent, myelocytes 4 per cent, lymphoblasts 1 per cent. The patient was discharged on July 24, 1935 with the advice that he should return for a biopsy of his prostate, but unfortunately he did not return and no further information is available about him.

*Case 2.* A white male (L. M.), aged 47, was admitted to the University Hospital on August 20, 1934 complaining of weakness and stiffness of his joints. Three years prior to admission, the patient stated, he had a swelling the size of a walnut in the left side of his neck for a period of two weeks. The mass was not tender and finally broke inside followed by a severe fever. His weakness continued and he had been in bed continuously the year before admission. Also one year before admission he complained of joint symptoms, including swelling and redness beginning in the right hand and fingers and then the elbows, left hand, knees and ankles. A residual stiffness had remained in the ankles, knees and the last three fingers on the right hand. He had lost over 100 pounds during the previous three years. The past history was otherwise negative.

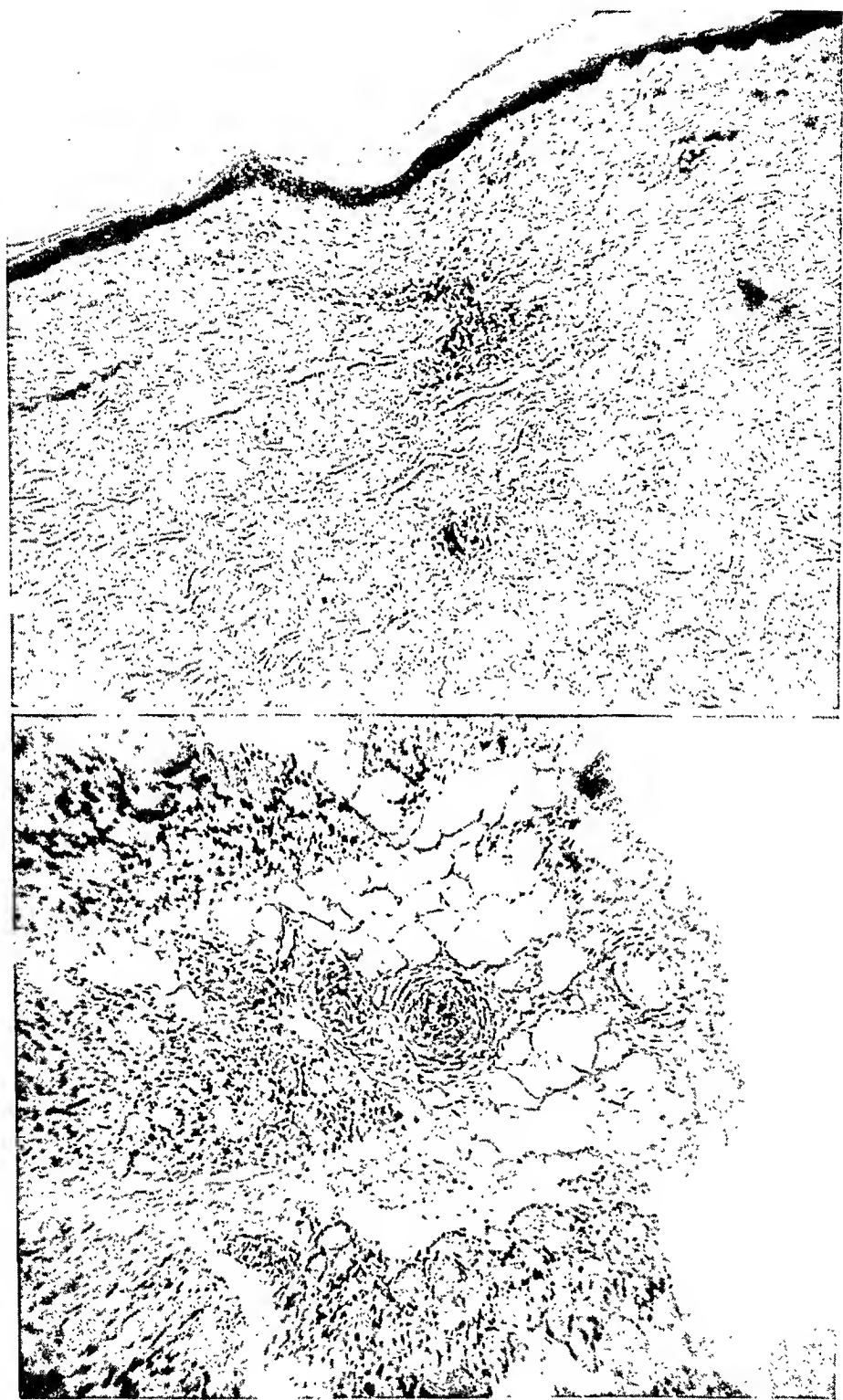
*Examination:* Showed a fairly well developed but markedly emaciated white adult male appearing chronically ill. The skin was dry and inelastic showing the evidence of marked weight loss. The mouth showed several teeth to be missing. The tonsils had been removed. The neck was negative except for small glands in the left posterior cervical chain. A few râles were heard at both lung bases posteriorly. Examination of the heart showed no enlargement. Examination of the abdomen showed the liver enlarged two fingers' breadth below the right costal margin. The spleen was felt three fingers' breadth below the left costal margin. The extremities presented typical fusiform swelling of the joints with marked emaciation and muscular atrophy. There was some limitation of motion in the joints, particularly in the latter three fingers of the right hand. The nails were rounded. There were small bilateral inguinal and axillary lymph glands and bilateral enlarged epitrochlear glands. Otherwise the physical examination was not significant.

*Laboratory findings:* The routine blood Kahn test and urine analysis were negative. Examination of the blood on August 20, 1934 showed hemoglobin 49 per cent, red blood cells 2.9 million, white blood cells 5,500 with 70 per cent polymorphonuclears, 19 per cent lymphocytes, 9 per cent monocytes, 2 per cent basophiles; the red blood cells appeared pale in color but were otherwise normal. On August 30, 1934 the hemoglobin was 55 per cent, the white blood cells, 11,000. On September 7, 1934 the hemoglobin was 43 per cent, red blood cells 2.19 million, white blood cells 5,100, with a differential count approximately as above. On September 13, 1934 the hemoglobin was 53 per cent, red blood cells 3.56 million, white blood cells 3,650; 78 per cent polymorphonuclears, 17 per cent lymphocytes, 3 per cent eosinophiles, 2 per cent basophiles. A calf muscle biopsy on August 24, 1934 showed slight atrophy of the skin. In the corium were occasional small perivascular infiltrations of lymphocytes, plasma cells and a few leukocytes (figure 2). The muscle showed atrophy, hypertrophy and variation in staining with an increase in the interstitial nuclei but no perivascular

FIG. 1. *Above* (Low power). Case 1. (B. R.) Age 67. Duration of arthritis 7 years. Loss of 25 pounds. Fusiform swelling of joints. Liver and spleen palpable. Hgb. 55 per cent; w.b.c. 2,850. The biopsy from the calf shows atrophy of epithelium, fibrosis of corium, and occasional small perivascular infiltrations in the corium.

FIG. 1. *A. Below* (Low power). Case 1. (B. R.) The voluntary muscle shows an increase in the interstitial nuclei and small perivascular infiltrations.





FIGS. 2-2 A.

infiltration (figure 2 A). Agglutination tests were negative for *B. typhosus*, *B. paratyphosis A* and *B*, *Br. abortus*, *Br. melitensis* and *Br. suis*. A stool culture showed no organisms of the typhoid dysentery group. Two blood cultures, one on admission and one shortly thereafter, were reported as negative. On September 19, 1934 a stereoscopic roentgen-ray of the chest was negative for parenchymal disease.

The patient had a persistent fever throughout his course in the hospital, varying from 99 to 101° F. daily. He was discharged September 21, 1934.

**Case 3.** A white female (B. T.), aged 34, entered the University Hospital April 6, 1935 complaining of rheumatism of six years' duration. She had been practically an invalid for two years previous to her admission. There had been a weight loss of 30 pounds in the six year period. The past history was uneventful.

**Physical examination:** Revealed a slender, undernourished, adult female. Her mouth was edentulous, her tonsils were absent, and her lung fields were clear. The joints presented typical fusiform swelling. There was ulnar deviation and some abduction of the right hand and a flexion deformity of both elbows. The spleen was palpable but the liver was not felt. There was flexion deformity of both knees with swelling and pain on motion. The ankles showed only stiffness.

**Laboratory findings:** Routine blood Kahn test was negative, and several urinalyses were all negative. The blood count on April 7, 1935 showed a hemoglobin of 58 per cent, 3,750,000 red blood cells, 3,100 white blood cells. The differential count showed 60 per cent polymorphonuclear cells, no basophiles, no eosinophiles and 40 per cent lymphocytes. No monocytes were present. Roentgen-rays of both knees on April 8, 1935 showed advanced atrophic arthritis with beginning erosion of the articulating surfaces of both knees, and beginning subluxation.

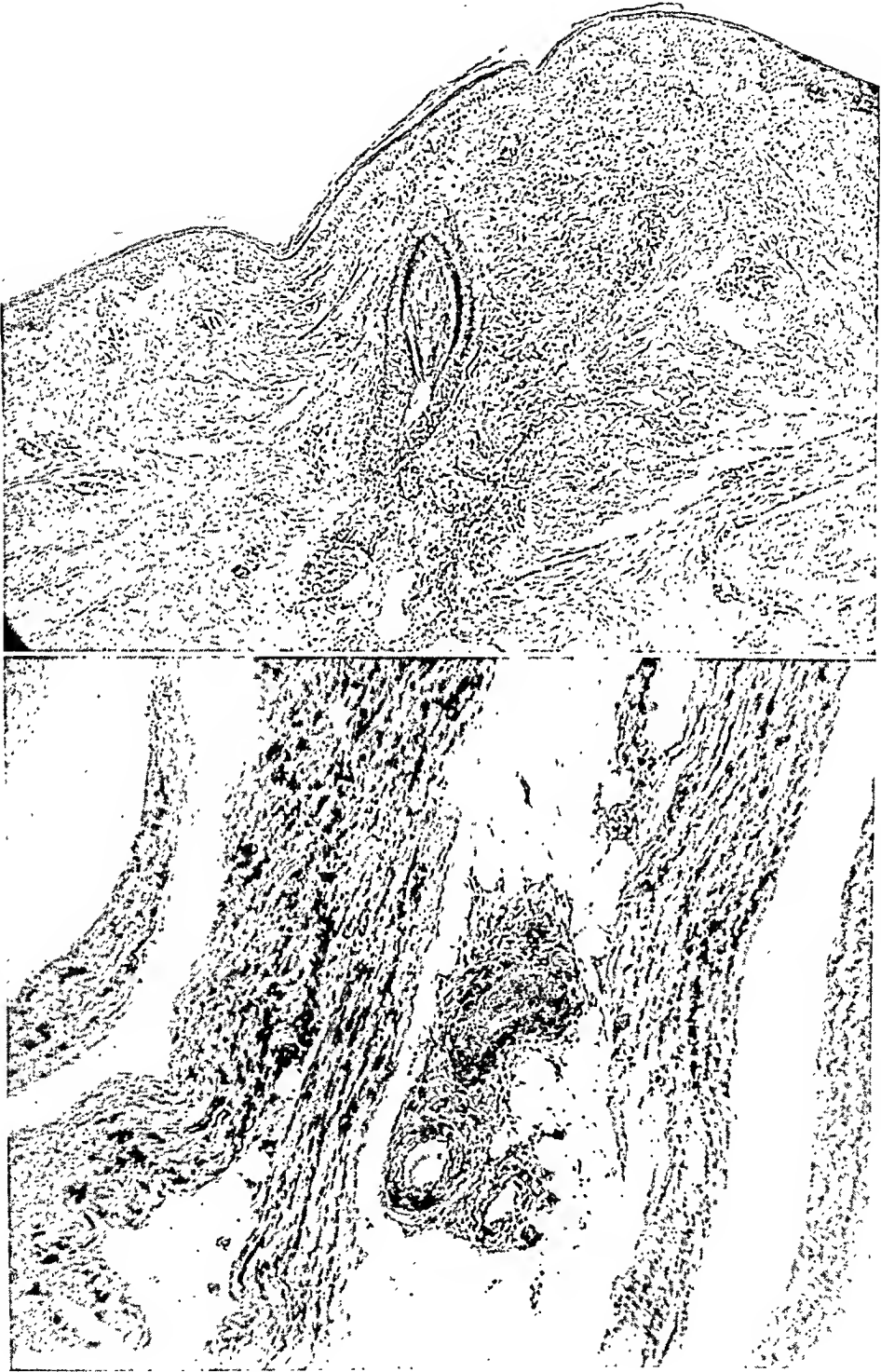
This patient's temperature varied from 99.5 to 101° F. for the first seven weeks that she was in the hospital. About May 25, 1935 her temperature gradually began to increase up to 102° F. daily, and on June 20, 1935 her temperature went to 104° F. This remained septic in type, daily reaching from 103 to 104° F. On June 11, 1935 a biopsy of the calf muscle was obtained which showed an atrophy of the epidermis and a number of small perivascular inflammatory foci in the dermis (figure 3). The muscle showed well marked changes with simple and fatty atrophy and small perivascular inflammatory foci, chiefly lymphocytic. A blood culture was taken on June 20, 1935, which was reported as showing *Staphylococcus aureus*. It was concluded, therefore, that some time about May 25, 1935 this patient had developed a septicemia. Her condition grew progressively worse and on July 1, 1935 her respirations ceased.

At autopsy the liver and spleen were both markedly enlarged. All muscles, including the heart muscle, were markedly atrophic. There was an acute abscess anterior to the vertebral column and posterior to the larynx, as well as a small abscess in the left lung. On microscopic section of the spleen, the following report was made: "Acute exacerbation of chronic passive congestion. Hyaline material, apparently amyloid, in many of the follicles. Numerous bone marrow giant cells in the sinusoidal spaces." All lymph nodes showed a chronic type of lymphadenitis with marked hyperplasia of the sinus reticulum. After decalcification, the sternum, vertebral body, and ribs showed a congestive marrow which was 90 per cent cellular. In one of the long bones there was fatty marrow associated with osteoporosis. The bone marrow from the femur was about 50 per cent cellular. Sections from the muscles of the thorax and back showed perivascular lymphocytic infiltration.

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FIG. 2. *Above* (Low power). Case 2. (L. M.) Age 47. Duration of arthritis one year. Weight loss of 100 pounds. Fusiform swelling of joints. Liver and spleen palpable. Anemia and leukopenia. The calf biopsy shows atrophy of the skin with occasional small perivascular infiltrations of lymphocytes, plasma cells and a few leukocytes.

FIG. 2A. *Below* (Low power). Case 2. (L. M.) The muscle fibers show simple and fatty atrophy, hypertrophy, variation in staining and an increase in the interstitial nuclei. No perivascular infiltrations are present.



FIGS. 3-4.

*Case 4.* A white male (B.S.), aged 64, was admitted to the University Hospital on August 3, 1937, with the chief complaint of rheumatism of nine years' duration. At the onset, he had noticed painful feet with swelling which lasted from three to four weeks. Since then, he had had recurrent attacks yearly, usually in the summertime. The attack noted on admission had started six weeks prior to that date, at which time he first observed swelling and pain in the left wrist and hand with loss of motion and some redness, leaving pain in the right sacroiliac area, the right shoulder and neck. He had lost 55 pounds in weight during the past nine years' time. His history was otherwise uneventful.

*Physical examination:* The patient was obviously undernourished and was in some acute distress. His temperature was 100.5° F. The spleen was palpable two fingers' breadth below the left costal margin, and the liver was palpable three fingers' breadth below the right costal margin. The wrists were swollen, warm and tender, and painful on motion. There was slight pain on motion of the elbows, shoulders and knees, but no swelling, warmth or limitation of motion.

*Laboratory findings:* Various urine examinations were entirely negative. The blood count on August 7, 1937 showed 62 per cent hemoglobin, 4,300,000 red blood cells, 2,200 white blood cells. The smear showed 18 per cent polymorphonuclear neutrophils, 70 per cent lymphocytes, and 4 per cent monocytes. The red blood cells were hypochromic, and the platelets were abundant. The white blood cell count on August 11, 1937 was 2,800. Stool examination was entirely negative, and blood agglutinations for *Brucella abortus*, *melitensis*, and *suis* were negative on August 9, 1937. The blood Kahn was negative. Chest roentgen-ray showed only pulmonary emphysema. A biopsy of a maxillary lymph node was obtained on August 17, 1937 which showed well-marked lymphoid hyperplasia. The follicular architecture was well preserved, suggesting that the process was apparently inflammatory. No biopsy of the skin or muscle was obtained.

## GROUP II

### *Rheumatoid Arthritis with Splenomegaly but without Leukopenia*

*Case 5.* A white male (W. T.), aged 27, was admitted to the University Hospital August 23, 1935 complaining of painful and swollen joints. Five years prior to admission he had an attack of influenza following which he developed a sharp pain beneath the right costal margin made much worse by deep breathing. Two months later he developed painful, red, swollen knee joints. Since that time all the joints of his body have become involved in a similar fashion. He had had a cough productive of about a quarter of a cupful of mucoid sputum daily which had occasionally been blood-tinged. He had lost a total of 40 pounds in weight during the past year. His past history was essentially negative.

On examination his temperature was 100, pulse was 130 and respirations were 30. The patient was an undernourished, white male lying in bed appearing chronically ill. The tonsils had been surgically removed. The lung fields were clear and the heart was negative. Blood pressure was 138 mm. of mercury systolic and 90 diastolic. In

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FIG. 3. *Above* (Low power). Case 3. (B. T.). Age 34. Duration of arthritis 6 years. Thirty pounds weight loss. Fusiform swelling of joints. Palpable spleen. Anemia and leukopenia. The calf biopsy showed a number of small perivascular inflammatory foci of lymphocytes and polymorphonuclear leukocytes in the skin. Very slight atrophy of the skin is present.

FIG. 4. *Below* (Low power). Case 6. (M. P.) Age 44. Duration of arthritis 10 years. Weight loss of 40 pounds. Fusiform swelling of joints. Liver and spleen both palpable. Hgb. 54 per cent, W.B.C. 13,450. The calf biopsy shows atrophy of the muscles and marked increase in interstitial nuclei. Small perivascular infiltrations can be seen about some of the arterioles.

the abdomen the spleen was just barely palpable beneath the left costal margin. The liver was not felt. Rectal examination was negative. There was generalized pea to bean sized firm lymphadenopathy. The joints showed extensive fusiform swelling with multiple flexion deformities.

*Laboratory findings:* The routine blood Kahn test was negative. Urinalysis on three occasions showed 1 to 2 plus albumin, a negative test for sugar, specific gravity of 1.020. Microscopic examination of the sediment showed one to two red blood cells per high power field, an occasional white blood cell and a few granular casts. Blood studies on August 22, 1935 showed a hemoglobin of 48 per cent (Sahli), with 3.46 million red blood cells and 9,100 white blood cells per cubic mm., with 72 per cent polymorphonuclears, 3 per cent eosinophiles, 20 per cent lymphocytes and 2 per cent monocytes. After iron therapy and one blood transfusion the hemoglobin on October 2, 1935 was 77 per cent (Sahli) with 3.77 million red blood cells per cubic mm. Two stool examinations showed a negative guaiac test, and 1-3 plus benzidine test for occult blood. Two sputum examinations showed no acid fast organisms. The blood non-protein nitrogen was 18 mg. per 100 c.c. on August 24, 1935. Blood cultures taken on September 4, 1935 and September 19, 1935 were both negative. Agglutination tests reported on September 6, 1935 were negative for *B. typhosus*, *paratyphosus A* and *B.*, *Br. abortus* and *Br. melitensis*. The patient was a type II in blood grouping. A throat culture showed *Streptococcus viridans*, *Streptococcus an-hemolyticus*, *Hemophilus hemolyticus* and a large gram positive micrococcus. Concentrated sputum examination for acid-fast bacilli was negative. Electrocardiogram on September 6, 1935 was reported as not definitely abnormal. A calf muscle biopsy on September 17, 1935 showed the absence of any inflammatory infiltrations in the skin. There was no increase in interstitial nuclei and perivascular infiltration. No changes were present which suggested angiomyositis. Stereoscopic roentgen-rays of the chest on August 26, 1935 and September 6, 1935 showed a negative chest. Roentgen-rays of the right elbow, right hand and right knee showed atrophic changes of all these joints. Bronchographic studies after the injection of iodized oil on October 14, 1935 showed no evidence of gross abnormality of the bronchi and no signs of bronchiectasis.

*Case 6.* A white female (M. P.), aged 44, was admitted to the University Hospital May 30, 1934 complaining of stiffness and deformity of the joints. Ten years before the patient had experienced swelling, redness, tenderness, and limitation of motion in the joints. Her first symptoms began in the ankles and later involved the wrists, finger joints, elbows, shoulders, knees and hips. In the last eight years there had been a progressive deformity of the above mentioned joints. She had remained up and about, being able to do most of her housework until six months prior to admission. At that time she developed influenza following which her rheumatism became markedly exacerbated, and walking became more difficult and painful. She had lost 40 pounds of weight.

*Physical examination:* Showed an emaciated patient appearing older than her actual age. All teeth had been recently extracted, and the tonsils had been removed. No adenopathy was present. The lung fields were clear and the heart was normal in size. The blood pressure was 126 systolic and 88 diastolic. The liver border was palpable two cm. below the rib margin. The spleen was definitely enlarged and could be felt below the left rib margin. There was fusiform swelling of the interphalangeal joints of both hands, the wrists and the knees, with some limitation of motion.

*Laboratory findings:* The blood Kahn test and urine analysis were negative. A blood count showed 54 per cent hemoglobin, 4.09 million red blood cells, 13,450 white blood cells; the differential smear showed 79 per cent polymorphonuclears, 2 per cent basophiles, 1 per cent eosinophiles, 15 per cent lymphocytes and 3 per cent monocytes. The red blood cells showed moderate acromia, but were normal in size and shape. The platelets were normal. A stool examination showed 1+ benzidine on a meat con-

taining diet. Stereoscopic roentgen-ray of the chest was negative. A roentgen-ray examination of the left knee showed chronic atrophic arthritis with definite atrophy of the tissue above and below the joint. Demineralization of the bone was present and there was a mild loss in the joint space. A biopsy of a calf muscle was done on July 12, 1934 and repeated on September 11, 1934. The first biopsy showed slight maceration of the epidermis. The dermis and panniculus showed no lesion other than operative hemorrhage. The voluntary muscle was distinctly abnormal. It was atrophic and the interstitial nuclei were increased. Around some of the small arteries there was a slight inflammatory reaction. The second biopsy showed some atrophy of the voluntary muscles. The muscle fibers were in part atrophic and in part hypertrophic. A definite increase of interstitial nuclei was present. The blood vessels showed a perivascular infiltration in several instances (see figure 4).

On August 5, 1934 the patient was discharged.

She returned to the University Hospital on September 10, 1934 without much change in her symptoms. Examination showed that her physical signs were approximately the same as at the time of discharge. The blood examination on September 10, 1934 showed 66 per cent hemoglobin, 4.1 million red blood cells, 7,500 white blood cells, and a differential smear showed polymorphonuclears 70 per cent, eosinophiles 4 per cent, lymphocytes 20 per cent, monocytes 6 per cent. The smear showed acromia of the red cells but otherwise was normal. October 22 the hemoglobin was 53 per cent, white blood count 7,350. Stool examination was negative.

*Case 7.* A white female (J. K.), aged 58, was admitted to the University Hospital on June 11, 1934, and discharged June 28, 1934. Her chief complaint was that of painful, deformed joints which she had had for four years. At the onset of her disease, she had had tenderness, swelling and painful motion of multiple joints, which included the joints of the hands, feet, knees and right shoulder, all of which had rapidly increased in severity six months prior to admission.

*Physical examination:* This patient was distinctly undernourished. The skin showed numerous pigmented, slightly elevated nevi over the abdomen and evidence of slight pallor. The teeth had been extracted. The tonsils were atrophic. The spleen was definitely enlarged, extending three fingers' breadth below the left costal margin. The liver was palpable one finger's breadth below the right costal margin. There was marked limitation in range of motion in both shoulders, more marked on the right. There was fusiform swelling of the elbows and wrists with moderate flexion deformity of both and distinct ulnar deviation of the hands. The knees were slightly tender to palpation.

*Laboratory findings:* Routine blood Kahn examination was negative and several urine analyses were all negative. The blood count on admission showed 60 per cent hemoglobin, 4,470,000 red blood cells, 10,950 white blood cells, and the differential count showed 84 per cent polymorphonuclear neutrophils, 1 per cent eosinophiles, 11 per cent lymphocytes, and 4 per cent monocytes. Stool examination was negative. A biopsy of the calf muscle was taken on September 6, 1934. There was both simple and fatty atrophy of the voluntary muscles. An active interstitial myositis was present with infiltrations around the small blood vessels and capillaries (figure 5). The arteries were of somewhat larger caliber and showed a definite periarteritis and angiomyositis. Roentgen-ray examinations of the bones of both hands showed chronic arthritis, of the mixed type, bilaterally. The carpal bones showed a fairly marked degree of calcium loss and apparent narrowing of interosseous joint spaces.

*Case 8.* A white male (F. K.), aged 56, was admitted to the University Hospital on November 28, 1934, and discharged on December 24, 1934. He gave a history of pain at various times for over a period of 18 years in different joints, including his hands, wrists, elbows, shoulders, knees, ankles, hips, back and neck. The initial attack was in the right hip. His condition had been progressively worse during the previous six years. For the six weeks prior to admission there had been some

swelling, soreness and pain in the right knee and hip, and he had been unable to walk for four weeks. He had lost a total of 12 pounds in the three months prior to admission. The history was otherwise uneventful.

*Physical examination:* This patient's weight was 110 pounds. Examination of the head and neck was negative. There was moderate submaxillary adenopathy bilaterally. No other enlarged lymph glands were noted. The spleen was palpable

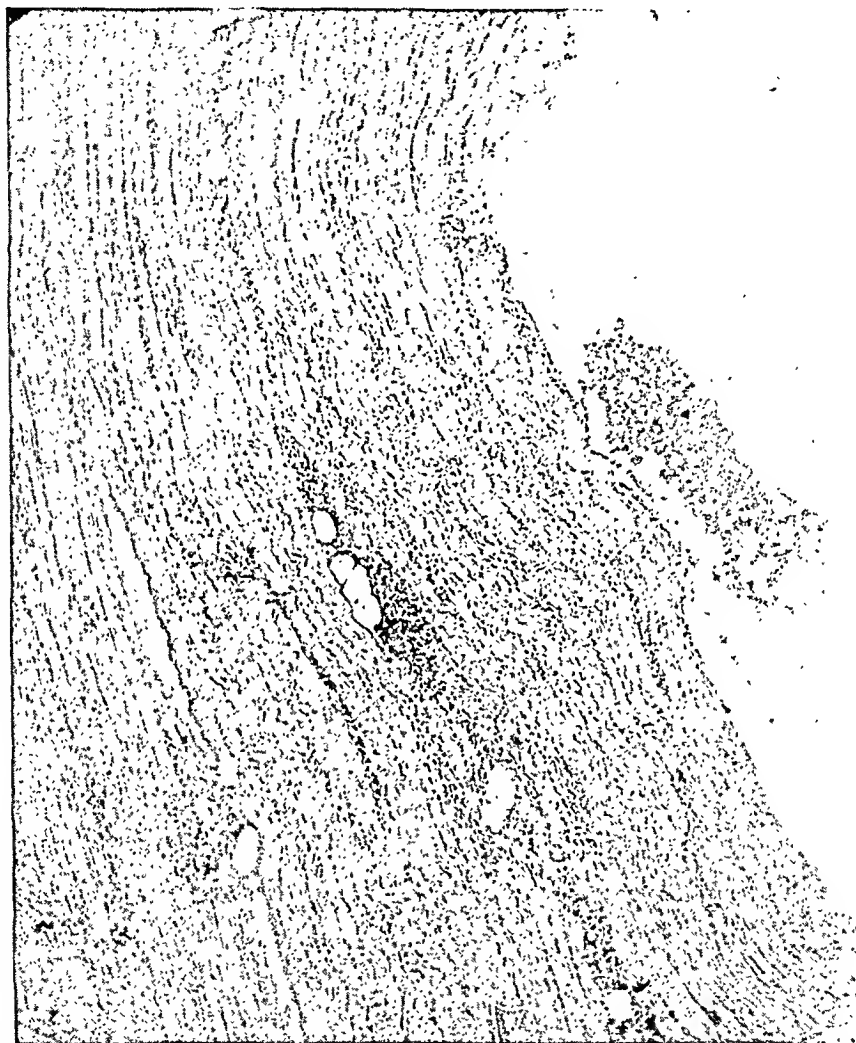


FIG. 5. (Low power). Case 7. (J. K.) Age 58. Duration of arthritis four years. Fusiform joint swelling. Spleen enlarged three fingers' breadth. Anemia, leukocytosis. The biopsy from the calf showed simple and fatty atrophy of the voluntary muscle. An increase in the interstitial nuclei is present. Several perivascular infiltrations of lymphocytes and leukocytes can be seen.

two fingers' breadth below the left costal margin. The liver was not felt. There was marked fusiform swelling of knees, hands, wrists, and toes. Complete flexion of the fingers and wrists was impossible. The motion of the left elbow was restricted from 90 degrees to about 120 degrees. The physical examination otherwise was negative.

*Laboratory findings:* The routine blood Kahn test for syphilis was negative, and several urine examinations were entirely normal. A blood count on December 2, 1934 showed 78 per cent hemoglobin, 4,600,000 red blood cells, 9,600 white blood cells. The



smears showed 70 per cent polymorphonuclear neutrophils, 2 per cent eosinophils, 24 per cent lymphocytes and 3 per cent monocytes. A basal metabolic rate was  $+10$  per cent. A biopsy of the calf muscle was done on December 11, 1934 and showed an occasional slight perivascular increase in wandering cells and a slight increase of interstitial nuclei, with evidence of clumping. The small vessels showed no significant lesion. Roentgen-rays of the right knee and left elbow showed mixed arthritis with osteoporosis of the bones of these joints. There was a fair amount of periarticular swelling of the right knee joint. Bony articular cortex was thin, and there was slight hypertrophic lipping of the external condyle.

### GROUP III

#### *Rheumatoid Arthritis, without Leukopenia or Splenomegaly*

*Case 9.* A white male (J. V. D.), aged 49, was admitted to the University Hospital on February 17, 1936 complaining of pain in his joints of 17 months' duration. The process had started in his ankles, but had within a few weeks involved the knee joints, right wrist, index and little fingers of the left hand, and all the fingers on the right hand. The left shoulder joint had also become painful, stiff and swollen. The process had been progressive up to the time of admission. He had lost 50 pounds of weight in the period since the onset of his illness. As a child, he had had measles, mumps, chicken-pox and whooping cough. There was no history of scarlet fever or rheumatic fever. He had had a tonsillectomy in January 1935, and all of his teeth had been extracted one year prior to admission.

*Physical examination:* Revealed an adult male who did not appear to be acutely ill. Examination of his head and neck was negative. The lung fields were clear and his heart was normal. The liver and spleen were not palpable. His knee joints, ankles, right wrist, and left index and little fingers presented the typical fusiform swelling of rheumatoid arthritis with stiffness. There was no redness present. The cervical, axillary, epitrochlear, and inguinal nodes were present but not enlarged or tender.

*Laboratory findings:* The routine blood Kahn test for syphilis was negative. Several urine examinations were entirely negative except for sugar, and the diagnosis of diabetes mellitus was eventually made. The blood count on February 18, 1936 showed 70 per cent hemoglobin, 4,190,000 red blood cells, 9,000 white blood cells; 50 per cent polymorphonuclear cells, no basophils, 3 per cent eosinophils, 45 per cent lymphocytes, and 2 per cent monocytes. A biopsy of the calf muscle obtained on February 25, 1936 showed very slight perivascular infiltration in the skin and no recognizable changes in the muscle. Stereoscopic roentgen-ray of the chest was entirely negative. No other roentgen-rays were obtained.

*Case 10.* A white female (M. R.), aged 47, was admitted to the University Hospital on January 31, 1936. Although her chief complaint was that of a vaginal tumor, she gave a history of having had "arthritis" since the age of four. This had become severe at the age of 14 following an attack of scarlet fever, and it was again accentuated following the delivery of her first child 13 years before admission. She had actually gained weight during the past three years. Pain and stiffness of her joints had been progressive during the previous 10 years.

*Physical examination:* Revealed submental, cervical, axillary, epitrochlear and inguinal gland enlargement. This was very mild, however. There was a cystic area present in the right breast. The extremities presented well marked fusiform swelling of the joints which involved the toes, fingers and hands primarily. However, the larger joints, such as the elbow, knee, shoulder, hip and ankle joints also showed some limitation of motion and pain. Pelvic examination was negative.

*Laboratory findings:* The routine Kahn test was negative. Repeated urine ex-



aminations were all normal. A blood count on January 31, 1936 showed 86 per cent hemoglobin, 9,500 white blood cells. On February 24, 1936 the hemoglobin was 75 per cent with 4,290,000 red blood cells, 5,750 white blood cells, 62 per cent polymorphonuclear leukocytes, no basophiles, 4 per cent eosinophiles, 20 per cent large lymphocytes, 6 per cent small lymphocytes, and 8 per cent monocytes. The red blood cells

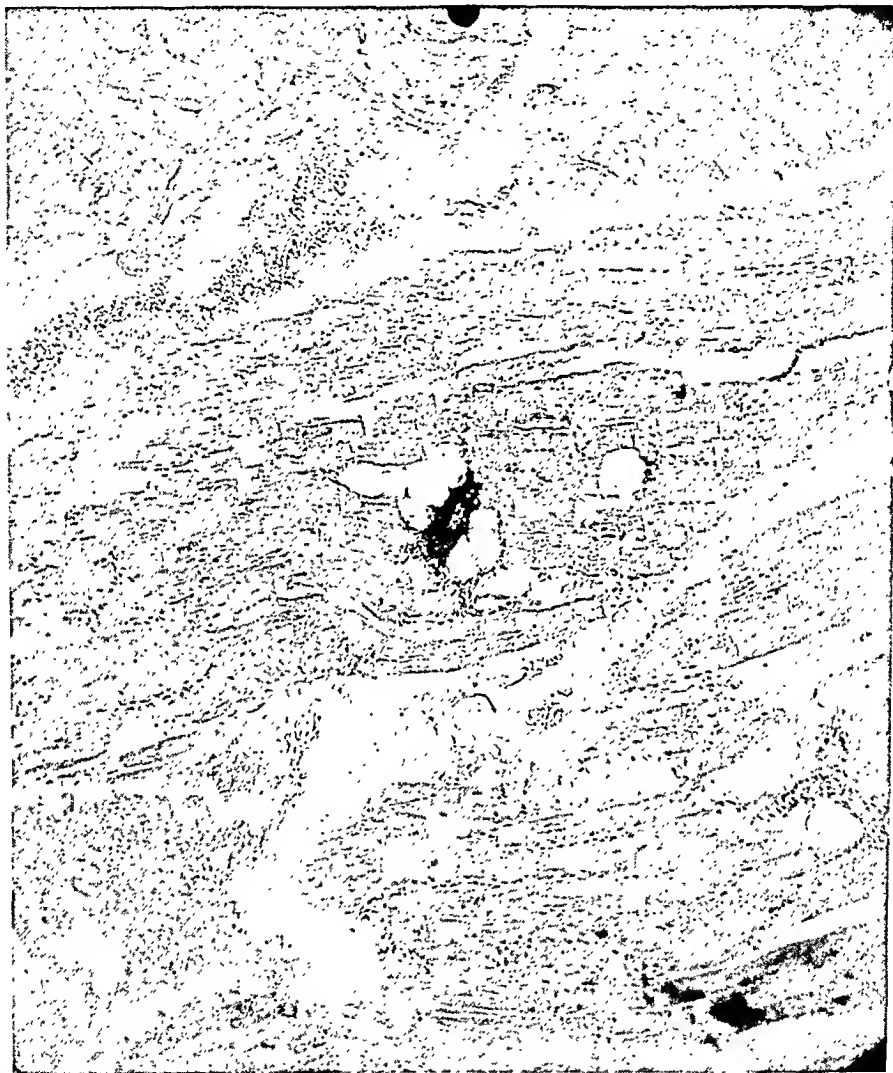


FIG. 6. (Low power). Case 10. (M. R.). Female, age 47, admitted January 31, 1936. Duration of arthritis 25 years. No weight loss. Fusiform joint swelling. No anemia. W.B.C. 9,600. Spleen not palpable. The biopsy from the calf showed several small foci of perivascular infiltrations in the muscle which were chiefly lymphocytic.

appeared normal. Stool examination was entirely negative. Roentgen-ray examinations of the right knee and spine showed advanced atrophic arthritis in each knee with considerable hypertrophic spurring, more on the right than on the left. There was minimal osteoporosis of the spine. There was advanced atrophic arthritis of both hip joints. A biopsy of a calf muscle on February 27, 1936 showed small perivascular lymphocytic infiltration in the skin and several small foci of perivascular infiltration in the muscle, chiefly lymphocytic, characteristic of an angiomylitis (figure 6).

This patient had a dilatation and curettage on February 4, 1936 which showed only polypoid hyperplasia. A tumor of the left breast, removed on February 8, 1936, showed a papilliferous cystadenocarcinoma. The patient had only a simple mastectomy, and the postoperative course was uneventful.

*Case 11.* A white male (J. M.), aged 53, was admitted to the University Hospital on February 26, 1936, complaining of arthritis in the knees and feet of four

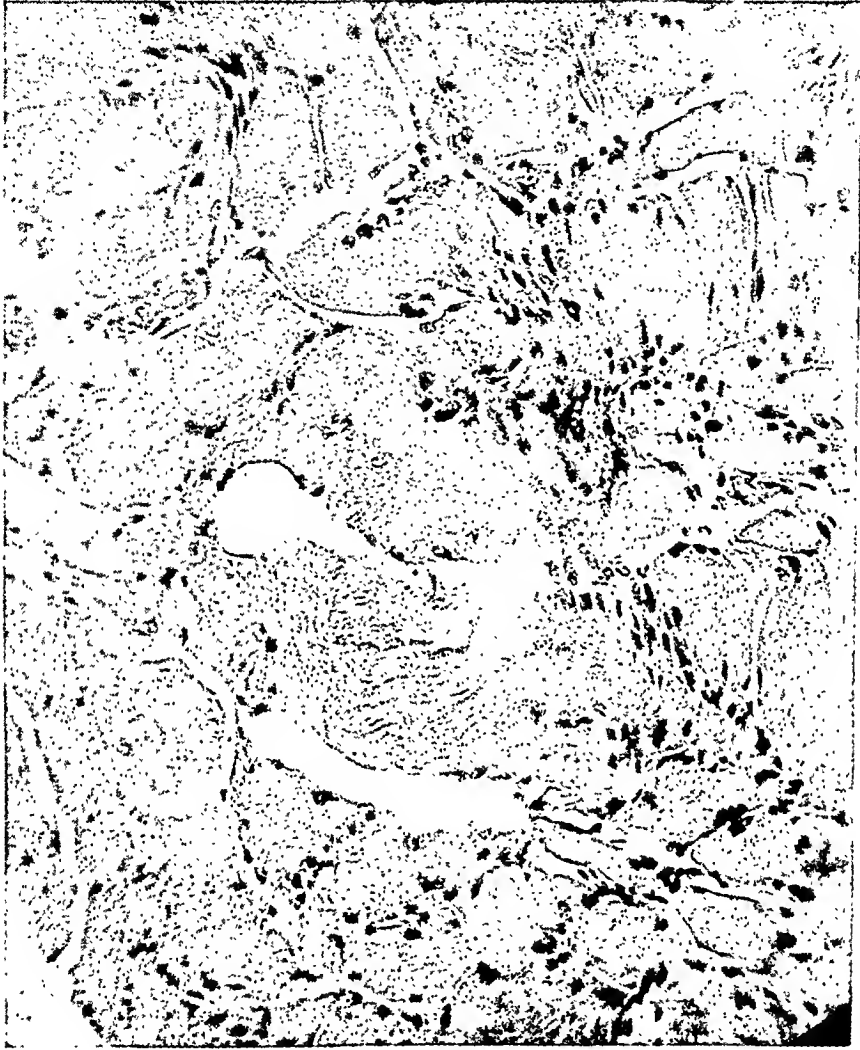


FIG. 7. (High power). Case 11. (J. M.). Male, age 54. Duration of arthritis three years. Fusiform joint swelling. Spleen not enlarged. Mild anemia. W.B.C. 21,850. A biopsy specimen shows irregular atrophy of the voluntary muscle. There is a marked increase in the interstitial nuclei and a slight old chronic myositis.

years' duration. He had originally developed pain and a fusiform swelling of the right knee, which had later spread to the left knee. Since that time, the ankles had become involved and subsequently almost all the joints of his body. The past history was otherwise uneventful.

*Physical examination:* Revealed an undernourished, adult male not acutely ill. The extremities revealed slight fusiform swelling of the fingers and wrists, and atrophy of the dorsum of the hands, with extensive fusiform swelling of both knees

and ankles. His examination was otherwise negative. The liver and spleen were not palpable, and there was no enlargement of the lymph glands noted.

*Laboratory findings:* The routine blood Kahn test was negative. His blood count showed a hemoglobin of 56 per cent, 5,640,000 red blood cells, 21,850 white blood cells. Differential smear showed 80 per cent polymorphonuclear cells, 10 per cent monocytes, 9 per cent basophiles and 1 per cent eosinophiles. The urine on admission showed a 1 per cent albumin, numerous white blood cells and 20 to 30 red blood cells per high power field. The diagnosis made was chronic pyelonephritis and hydro-ureter, in addition to a chronic active prostatitis. A biopsy of the calf muscle, obtained on March 3, 1936, showed us significant changes in the skin. There was irregular atrophy of the muscle with increased stroma cells and a still active chronic myositis. The inflammatory process was non-selective for the vessels (figure 7). His white blood cell count later returned to 10,550 before his discharge. Roentgen-rays of the knees showed the arthritis, involving both knees and both feet, primarily atrophic in type.

*Case 12.* A white male (R. A.), aged 36, was admitted to the University Hospital June 1, 1936, complaining of pain, swelling and stiffness of the joints. The attacks of swelling, heat, redness, and tenderness of the joints began at the age of 11 at which time he was confined to bed for one year. On admission the most painful joints were the elbows, shoulders, and right knee. All the joints involved were stiff with marked limitation of motion. He had lost 70 pounds during the one and one-half years prior to admission, during which time he had had occasional "fever." The history otherwise was negative.

*Physical examination:* Revealed an undernourished white adult male, chronically ill. All the joints except the spine showed fusiform swelling. There was a flexion deformity of the elbows and knees. The arms were held at the side and the hips were extended. Heart and lungs were negative. The liver and spleen were not palpable and there was no lymphadenopathy. The examination was otherwise non-essential.

*Laboratory findings:* Routine blood Kahn test was negative. Several urine examinations were negative. Complete blood count on admission showed 89 per cent hemoglobin, 5.4 million red blood cells, and 7,200 white blood cells. The differential count showed 60 per cent polymorphonuclears, 1 per cent basophiles, 1 per cent eosinophiles, 24 per cent lymphocytes and 14 per cent monocytes. A biopsy of a calf muscle on June 16, 1936 showed the dermis was without inflammatory reaction; there was a slight fatty and simple atrophy of voluntary muscle with a relative increase in interstitial nuclei; numerous phagocytes with hemosiderin in them were seen around the small blood vessels, suggesting a previous local hemorrhage.

## DISCUSSION

*Splenomegaly in Arthritis.* Although Felty first described the entire complex, its several features have been recorded separately by others. Chauffard<sup>12</sup> in 1896, and Herringham<sup>13</sup> in 1909, described splenomegaly and hepatomegaly in association with arthritis. Still<sup>14</sup> in 1897 described a syndrome, seen in children, of anemia, enlarged glands and enlarged spleen in association with chronic progressive enlargement of the joints, which has since been called "Still's disease." Giffin,<sup>15</sup> in writing of diseases of the spleen, stated that splenomegaly sometimes occurs in chronic arthritis and called it chronic infectious splenomegaly. Ward<sup>16</sup> described a leukopenia and a low grade eosinophilia occurring in chronic septic splenomegaly. McCrae,<sup>17</sup> in 1904, reported an enlargement of the spleen in four of 110 cases of arthritis deformans: Hench<sup>18</sup> found that splenomegaly occurred

in about 1 per cent of the cases of rheumatoid arthritis, and Dawson<sup>19</sup> reports that it occurs in between 10 and 15 per cent of the cases.

The pathological findings in the spleen in cases of "Felty's syndrome," where splenectomy has been performed or autopsy done, show great similarity. Hanrahan and Miller<sup>2</sup> described hyperplasia of the endothelial cells lining dilated sinuses, an increased number of plasma cells in the pulp spaces, and very large Malpighian bodies with germinal centers in proportion. Craven's<sup>5</sup> case showed dilated sinuses filled with red blood cells. The splenic pulp had many plasma cells and large mononuclear phagocytes. The Malpighian bodies were enlarged with prominent germinal centers. Price and Schoenfeld<sup>6</sup> and Reich<sup>10</sup> described a diffuse chronic splenitis. Singer and Levy<sup>8</sup> likewise described the findings of a chronic septic splenitis in their two cases.

Whereas eight of the 12 cases described above in our series had an enlarged spleen in association with their rheumatoid arthritis, there is a microscopic study of the spleen available on only one. This was Case 3 described under Group I. This patient came to autopsy and the pathologist submitted the following description of the spleen: "Hyalin material, apparently amyloid, in many of the follicles. Numerous bone marrow giant cells in the sinusoidal spaces."

None of the pathologic findings in the spleens of our cases and those described by others are indicative, we believe, of anything more than a chronic infection, most probably of a generalized nature.

*Leukopenia in Arthritis.* In six of the 110 cases of arthritis deformans reported by McCrae,<sup>17</sup> a leukocyte count of 5000 or less was recorded. Eaton<sup>20</sup> found a leukopenia in 22 per cent of 250 cases, the differential formulae showing a neutropenia (under 60 per cent) in 43 per cent and an eosinophilia in 10 per cent. Dawson<sup>19</sup> reports that a leukopenia often develops in long continued chronic cases of rheumatoid arthritis and Hench<sup>11</sup> likewise states that in the more chronic stages the leukocytes tend to be definitely low (4000 to 6000 per cu. mm.).

The duration of the rheumatoid arthritis in the four cases of this group of 12 which showed a leukopenia was eight, one, six, and nine years respectively. Although the average duration of disease in these 12 cases was 6.9 years, we agree with those who believe that the leukopenic response is indicative of a long standing chronic infection, and not an integral part of any specific syndrome.

*Bone Marrow Response.* The sternal bone marrow in the case reported by Price and Schoenfeld<sup>6</sup> showed some hyperplasia, a few bone marrow giant cells, and an active myelosis. The bone marrow in one of the two cases reported by Singer and Levy<sup>8</sup> showed marked congestion and signs of atrophy in the fatty portions. The reticulum was inconspicuous and the cellularity was 37 per cent. The marrow of the other case showed dilated sinuses and congestion. The reticulum cells were swollen and the cellularity was 80 per cent. A sternal puncture in Williams' case<sup>9</sup> showed numerous

normoblasts and nucleated red blood cells. There were some stem cells, a few granulocytes, rare mature polymorphonuclear leukocytes, and numerous megakaryocytes. The atypical findings in the bone marrow of Williams' case<sup>9</sup> suggested to him a primary blood dyscrasia, in which there is an arrest in the maturation of the polymorphonuclear leukocytes.

A specimen of bone marrow was obtained in one case of this series, Case 3 in Group I, which patient came to autopsy. After decalcification the rib, sternum and vertebral body showed bone marrow which was actively cellular, having numerous megakaryocytes and the various types of young blood cells. The cellularity varied from 60 to 80 per cent.

Whereas the number of cases with bone marrow findings reported elsewhere when added to our own is very small, the picture found in these few does not seem characteristic to us of anything other than the result of a chronic infection.

*Lymph Glands.* A biopsy of a lymph gland in one case reported by Felty<sup>1</sup> showed chronic lymphadenitis. The hemolymph nodes in Price and Schoenfeld's case<sup>6</sup> showed myeloid changes with moderate edema and deposits of hemosiderin. An inguinal node biopsied in one of the two cases reported by Singer and Levy<sup>8</sup> showed chronic lymphadenitis. In the other case, dilated sinuses and hyperplasia were found in the abdominal, inguinal and cervical glands.

Two of our cases have a microscopic study of a lymph gland recorded. One case (Case 4, Group I) showed a chronic hyperplastic lymphadenitis with marked hyperplasia of the sinus reticulum. The lymph gland of the other case (Case 2, Group III) showed chronic hyperplastic lymphadenitis with marked hyperplasia of the reticuloendothelium.

We do not consider the changes found in our own cases, or in the others reported, as significant of anything other than a chronic infection, not of any specific nature.

*Calf Muscle Biopsies.* In Group I of our series, three of the four cases showing rheumatoid arthritis, splenomegaly, leukopenia and adenitis (Cases 1, 2 and 3) showed on biopsy of the skin and calf muscle: (1) atrophy of the epithelium; (2) fibrosis of the corium; (3) increase in interstitial nuclei of the muscle fibers, and (4) small perivascular infiltrations throughout the corium and muscle. It may be reasoned that the atrophy, fibrosis, and increase in interstitial nuclei are the result of disuse in these cases of long standing arthritis, yet we believe that these three features may likewise be manifestations of a chronic generalized infection. We further believe that the perivascular infiltration found in the corium and muscle more conclusively points toward the presence of some generalized infectious process.

The patients in Group II (Cases 5, 6, 7 and 8) were selected because they presented, in addition to chronic rheumatoid arthritis and splenomegaly, a normal or elevated leukocyte count instead of a leukopenia. Calf muscle biopsies on all four of these cases showed two with an atrophy of the epithelium, fibrosis of the corium, increase in interstitial nuclei and again the

perivascular lymphocytic infiltration. In other words, the pathologic findings in these two groups are almost identical even though the cases of Group II lack the leukopenia.

Again, as another means of control for the patients in Group I, we selected four cases (Group III, Cases 9, 10, 11 and 12). These four cases all showed a chronic rheumatoid arthritis, but without any splenomegaly or leukopenia. The calf muscle biopsies of these four cases showed atrophy, fibrosis and increase in the interstitial nuclei and, in addition, Case 9 showed a slight perivascular infiltration, Case 10 showed definite small foci of perivascular infiltration, chiefly lymphocytic, and Case 11 showed an old chronic myositis which is still active.

In summarizing these pathologic findings, we believe that the changes noted in Cases 1, 2 and 3 of Group I, Cases 6 and 7 of Group II, and Cases 9, 10 and 11 of Group III are practically identical and therefore indicative of the same generalized chronic infectious process regardless of the variation in the clinical picture of these three groups.

We likewise believe that the incidence noted in the literature of leukopenia occurring in chronic rheumatoid arthritis, and of splenomegaly in chronic rheumatoid arthritis is of such an extent that the factor of this combination (arthritis, splenomegaly, leukopenia) occurring together in the same patient, is a result of chance rather than indicative of any specific syndrome. We therefore concur with the viewpoint of Dawson<sup>19</sup> and others that there is no justification for the segregation of these cases, and that the use of the term "Felty's syndrome" should be discontinued.

### CONCLUSIONS

1. Calf muscle biopsies from patients showing chronic arthritis, leukopenia, and splenomegaly, presented a similar pathologic picture to that seen in biopsies from those cases showing only chronic rheumatoid arthritis.
2. The disease process in cases of chronic rheumatoid arthritis either with or without leukopenia and splenomegaly is a generalized one.
3. Inasmuch as leukopenia or splenomegaly is not infrequent in patients with chronic rheumatoid arthritis, the occurrence of "Felty's syndrome" in patients with arthritis is but a matter of chance.
4. We believe Felty gave the correct interpretation to the syndrome when he said "the several features are manifestations of one pathological process caused by a noxa which simultaneously affects the joints, the spleen and the blood leukocytes." This "noxa" seems to be the unknown etiological agent of rheumatoid arthritis and the whole syndrome is a not unexpected complex.

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## SUBCLINICAL PULMONARY TUBERCULOSIS; A PRESENTATION OF FORTY CASES\*

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THE individual destined to develop pulmonary tuberculosis will in most instances have it diagnosed no earlier today than years ago. Though the death rate continues to show a yearly drop, evidence indicates that this favorable occurrence has resulted from factors other than an early diagnosis.<sup>1, 2, 3</sup> Efforts in the past have been directed primarily toward studying disease in its later stages as it occurs at the bedside, when symptoms and physical signs have made their appearance, and later, unfortunately, in a still more advanced stage, at the postmortem table. Relatively little is known at present of sub-clinical disease, of methods for its discovery, or of the factors that determine its subsequent course. This field is wide and unexplored, and a scientific approach to it offers the medical profession the privilege of serving mankind more adequately by making possible the treatment of disease in its early rather than in its later stages.

Because illness and health continue to be associated with the presence or absence of symptoms and signs, our mental habits make it difficult to treat and consider seriously the potentialities of a pathological process not yet extensive enough to alter the individual's well being. The fallacy of associating disease only with its manifestations as they occur later in the course was well appreciated and probably best expressed over a century ago by a French physician, Gaspard Laurent Bayle, when he wrote of tuberculosis: "This manner of considering phthisis is just as ridiculous as that of a naturalist who seeing a young oak tree would refuse absolutely to give it this name because it did not yet show all its generic and specific characteristics. Moreover the oak which has just grown out of the ground, although it is a very feeble plant, is none the less a tree whose trunks will acquire a great deal of strength. It is the same with phthisis: in the beginning it seems scarcely a slight indisposition: in its last stage it strikes down the strongest man, it devours, consumes and reduces to a skeleton those whose plumpness, freshness, and health appeared unalterable."

Tuberculosis as it affects the individual will always continue to be a very serious personal problem. A falling death rate in the general population offers little solace to the victim of tuberculosis who did not have the advantage of early diagnosis. For him the problems of treatment are multiplied, require a longer period of cure, and give a prognosis that is definitely less favorable.

To insure early diagnosis all the infected, as determined by a properly

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administered Mantoux test, must be examined by the roentgen-ray at regular intervals, either by film or fluoroscopy.<sup>1</sup> At the present time, unfortunately, known tuberculous infection is not seriously enough considered. Since, among infected students under observation in the period from 1933 to 1939, 1.6 per cent of the infected were found with already active tuberculosis on admission to the university or developed it subsequently, it is reasonable to assume that at least 10 per cent of the infected will develop active demonstrable disease during their life time. The fact is appreciated that all the infected do not react to the Mantoux test,<sup>4</sup> but to date, in over 20,000 students who have been tuberculin tested, no individual negative to tuberculin has reported to the student clinic and been found to have active tuberculosis. The recent work of Lumsden<sup>5</sup> concerning the adequacy of the tuberculin test in determining infection deserves to be considered; but until individuals with active minimal or subminimal tuberculosis are found who fail to react to tuberculin the test will continue to be of great practical value in making examination necessary only for those showing a positive reaction. With the advent of large group surveys the tuberculous lesion is being found in its earliest visible form, and, once found, the question regarding its status immediately arises.

#### THE EARLY INFILTRATE

The problem of the early pulmonary infiltrate is to determine whether it is pathologically active or healed. The determination of the status of the early lesion, now more frequently being found when no larger than 3 to 10 millimeters in diameter, or present in the form of so-called apical "caps" or pleuritis, cannot be done without considerable effort and without often repeated examination. Such lesions, though occurring in apparently healthy individuals and frequently considered of no consequence, are in fact pathologically active as determined by laboratory methods. Even though these laboratory studies prove to be negative at first, where such lesions have been found, they should continually be viewed with suspicion, and detailed examinations should be repeated at intervals of three to six months. In the past reliance usually has been placed on serial roentgen-ray films. But entire dependence upon roentgen-ray films is not without objection, for a process may be active, as indicated by the presence of tubercle bacilli in the gastric contents, and yet may show no significant roentgen-ray change for a period of years. The process is, however, potentially dangerous. Moreover, with serial films as the only measure of activity, further lung invasion and destruction are frequently allowed to occur and the prognosis is made less favorable.

The minute size of the early infiltrate gives no assurance of benignity. An active lesion, though small, repeatedly seeding tubercle bacilli in the surrounding tissues, offers the constant and dangerous threat of progressive tuberculosis. It becomes important, therefore, to take immediate advantage of all methods which give additional information regarding the exact status

of the lesion and the course it may subsequently pursue. Unfortunately, at the present time, because observation has been limited to relatively few cases, little is known regarding the early lesion and whether its course is usually benign or progressive. Furthermore, little is known of the factors that may alter its course.

### PROCEDURE

Individuals showing small infiltrates, either by roentgenogram or fluoroscopy, are hospitalized for a short period, at which time a history is taken, a complete physical examination is made, and the temperature and pulse, though seldom found elevated, are determined at four-hour intervals. Laboratory studies consist of aspiration of the fasting morning gastric contents,<sup>6</sup> determination of the blood sedimentation rate according to the method of Cutler,<sup>7</sup> and repeated study of the total and differential blood counts. The sputum is routinely studied, but in early cases tubercle bacilli are rarely found by this method of examination.<sup>6</sup>

The fasting gastric contents are aspirated on three successive mornings by means of a size 16 French nasal catheter, passed either through the nose or by mouth. By means of a Luer syringe from 10 to 15 c.c. of gastric contents are usually obtainable. If nothing can be aspirated, 15 c.c. of sterile normal saline are placed in the stomach by means of the tube, and after 15 minutes this fluid is again withdrawn, placed in a sterile container, and sent to a laboratory for examination by direct stain and guinea pig inoculation. This method is more satisfactory than the usually advocated gastric lavage. The large amount of fluid obtained by lavage is cumbersome to handle, especially if the specimen must be sent to the laboratory by mail, and is also less easily prepared for examination. It should be added that the tube, syringe and specimen bottle should always be sterilized by boiling for at least 20 minutes before being used. In our series of over 70 cases, showing lesions which were minimal or subminimal in extent, the sputum when obtainable was negative in all instances, whereas direct stains of the centrifuged gastric contents were positive in 18 per cent, and guinea pig inoculation with gastric centrifugate gave positive findings in 72 per cent of the cases. In moderately or far advanced active cases, when at least three aspirations are done, on no occasion has a negative result been obtained.

The adequacy of gastric aspiration combined with guinea pig inoculation has not been widely appreciated, nor has sufficient use been made of this valuable method of examination. Experience shows that:

1. If positive, it establishes the diagnosis and indicates whether any lesion is active.
2. It is the best indicator that the minimal and subminimal lesions are tuberculous and active.
3. It is an important aid in differential diagnosis.
4. It is the most accurate gauge in measuring the success of treatment and how long treatment should be continued.

5. It is an important factor in considering the need of surgical treatment.
6. It is a measurement of infectiousness and helps determine the patient's relationship to society.
7. It makes possible a more accurate prognosis.

Determination of the *blood sedimentation rate* is a relatively simple laboratory procedure. No corrections were made for anemia, for in no instance did this exist to an appreciable degree. The sedimentation rate, though showing an increase before the temperature is elevated or before symptoms are manifest, is usually found, as will subsequently be shown, to be normal in the early stages of tuberculosis.

Concurring in Medlar's<sup>8</sup> thesis: "The only logical way to determine whether the leukocytic reaction in the tuberculous is of real significance is to compare the interpretation of the leukocytic picture with the interpretation of the status of a case as judged by the clinical progress and by roentgenographic findings," the leukocytic picture was studied and correlations made with other laboratory methods.

The leukocytic reaction has been interpreted as determined by the Medlar leukocytic index.<sup>9,10</sup> Graphic representations of the total number of neutrophils, lymphocytes and monocytes have also been made. Medlar's method of interpreting the leukocyte reaction has been chosen in preference to the methods of Blackfan,<sup>11</sup> Cunningham<sup>12</sup> and Webb<sup>13</sup> in whose interpretations the monocytes and lymphocytes or their ratios alone are considered.

Many of the leukocyte counts showed no marked variation over a period of months, or at least not enough change to be considered as significant. In these instances (table 1) the average Medlar index of the total number of weekly counts adequately indicates the leukocyte response. To better portray the leukocyte reaction in certain cases, the entire series of weekly counts are presented separately.

The blood counts were done by an especially trained technician and the students studied reported at the same designated hour and day at weekly intervals. The patient, on reporting for the test, was requested to rest on a bed for at least one-half hour before blood for examination was taken.

## METHOD

For the total count, blood from an ear puncture was diluted 1 to 20 with 1 per cent acetic acid in pipettes certified by the National Bureau of Standards. The pipette was shaken one-half to one minute immediately after the dilution of blood, and two to three minutes before filling the counting chamber (Spencer's Bright-Line Improved Neubauer Chamber; cover glasses, size 20 by 24 mm., thickness 5 mm.; all certified by the National Bureau of Standards). Two pipettes were used for each count, filling one chamber from each pipette, after discarding three drops and counting the four large-ruled corner squares in each chamber. If the number of cells counted in one chamber varied by more than 10 from that in the other chamber, the pipettes were reshaken and the chambers filled again. The average of the cells counted from both pipettes was multiplied by 50 to obtain the total number of white cells per cubic millimeter of blood.

TABLE I  
Presentation of Data

Case Age	Period of Observation Weight	Blood Sedimentation Rate		Leukocyte Reaction		Gastric Aspiration with Pig Inoculation		Roentgen-Ray Study
		Date	Rate	No.	Ave. Medlar Index	Date	Result	
1 Hoge 73876 22	10-14-38 to 5-27-39 Wt. Stat.	10-14-38 11-14-38 1-20-39 4-12-39	1 4 3 3	9	34.8	Feb. 1939	+	Thoracoplasty with good collapse. Surgical treatment not successful in converting gastric contents.
		Average	2.8		10-14-38 to 4-12-39			
2 Norv 75764 24 M.	9-19-38 to 1-13-39 Wt. Stat.	10-17-38 1-13-39	1 2	12	18.1	Nov. 1938	+	Small soft infiltrate in both clavicular areas. Rapid retrogression of lesion following institution of San. treatment.
		Average	1.5		10-14-38 to 1-13-39			
3 Luer 77106 22 M.A.	4- 2-36 to 1-19-39 Wt. Gain 29 lb.	4- 9-36 10-25-37 12- 4-37 1-17-39	13 13 6 7	25	17.1	Apr. 1936 Oct. 1937 Feb. 1938 June 1938 Jan. 1939	++ ++ ++ ++ ++	Bilateral apical and clavicular lesion with marked retrogression under San. regimen. Fibrotic lesion persists which shows no recent significant change.
		Average	9.8		10-25-37 to 6- 6-38			
4 Land 77192 18 M.A.	2- 3-37 to 6- 2-39 Wt. Gain 16 lb.	2- 3-37 10-25-37 10-17-37 5-17-38 4-15-39	10 7 1 10 8	51	34.2	Feb. 1937 Nov. 1937 May 1938 Nov. 1938 Feb. 1939	++ ++ 0 ++ ++	Lesion first noted 1933 with periods of retrogression and extension. Left pneumothorax instituted 1937 apparently with excellent results. Because of persistent free bacilli, pneumothorax is being instituted on right this summer. (1939)
		Average	5.2		2- 3-37 to 6- 2-39			
5 Gree 79975 20 M.A.	9-18-33 to 3-29-37 Wt. Gain 11 lb.	2- 7-36 6-20-36 2-10-37 3-29-37	17 19 15.5 21	10	28.7	Feb. 1937 June 1937 Feb. 1938	++ ++ ++	Progressive lesion resulting from first infection. Returned to Univ. on two occasions because of satisfactory clinical picture. Unfavorable subsequent course on each occasion.
		Average	18.1		2- 6-36 to 3-31-37			
6 Ann 79831 18 M. to M.A.	9-16-33 to 6- 8-37 Wt. Gain 23 lb.	10-13-34 12-21-34 2-20-35 2- 3-36 6-15-36 10-14-36 3- 3-37 6- 5-37	11 8 8 11 9 10 13 11	23	Separate Presentation	Mar. 1936 Dec. 1936 May 1937	++ ++ ++	Massive pleural effusion in Dec. 1933 with subsequent development of progressive tuberculosis from subminimal apical lesion. Process has never caused symptoms subsequent to effusion, and recent films April 1939 show continued change.
		Average	10.1		3- 3-37 to 6- 8-37			
7 Aud. 82226 20 M.	9-26-34 to 1-18-35 Wt. Gain 24 lb.	10-20-34 4- 5-35 3-24-36 6- 2-36 11- 5-36 5-24-37 11-16-38 3-16-38 11-16-38	3.5 2 4.5 5 6 8 9 5 4	33	20.4	Mar. 1938 Nov. 1938	++ 0	Disseminated lesions in both apices and clavicular regions showing alternate periods of extension and retrogression.
		Average	5.3					
8 Gloz 82916 18 M.	9-21-34 to 3- 2-38 Wt. Gain 14 lb.	9-10-34 3-12-35 11-27-35 2-22-36 5-27-39 12- 8-36 3-23-37 10- 6-37 2-23-38	15 7 9 10 9 8.5 11 12 5.5	21	24.5	Oct. 1934 May 1935 Oct. 1936	++ ++ 0	Minimal infiltrate at right apex with subsequent healing by fibrosis and calcification.
		Average	9.6		12- 9-36 to 6- 1-38			

TABLE I—*Continued*

Case Age	Period of Observation Weight	Blood Sedi- mentation Rate		Leukocyte Reaction		Gastric Aspiration with Pig Inoculation		Roentgen-Ray Study
		Date	Rate	No.	Ave. Medlar Index	Date	Result	
9 Clem 83312 25 M.	9-22-34 to 1-13-39 Wt. Gain 16 lb.	5-16-36 1-14-37 10- 3-37 4-12-38 9-23-38 6-24-38 1-13-39	11 2 4 3 3 3 3	31	23.8      10- 4-37 to 1-13-39	May 1936 Dec. 1937 May 1938 Sept. 1938 Jan. 1939	+ 0 0 + +	Subminimal lesion first noted in 1934. Extension in 1936. Subsequent Sanatorium treatment with retrogression. Slow extension since Sept. 1938. Return to Sanatorium July 1939.
10 Sven 84566 34 M.	10-17-34 to 5- 6-39 Wt. Gain 25 lb.	10-17-34 1-23-35 12-28-35 9-30-36 4-20-37 11- 2-37 3-11-38 5- 1-39	2 5 4 3 5 9 3.5 3.5	12	12.3      11- 9-38 to 5- 1-39	Dec. 1936 Apr. 1937 Mar. 1938 May 1939	+ 0 0 0	Sanatorium treatment prior to 1934. Residual infiltrate right clavicular region with extension in Dec. 1936. San. treatment with retrogression of lesion. Recent films, June 1939, show only calcification.
11 Soff. 87246 21 M.	9-21-35 to 5-31-38 Wt. Gain 20 lb.	4- 6-37 5-10-37 6- 7-38 10-13-37 5-29-38	7 10 7 5 3	37	62.9 Septic picture completely at variance with gast. cont. and x-ray. 2- 7-37 to 5-23-38	Apr. 1937 June 1937 Apr. 1938	0 0 0	Minimal right clavicular infiltrate first noted Sept. 1935. Some extension Feb. to May 1937. Retrogression, May 1937 to June 1938. Recent film, July 1939, shows further retrogression.
12 Lair 87375 20 M.	12- 8-37 to 6- 5-39 Wt. Gain 13 lb.	1-16-38 3-19-38 5-11-38 6-11-38 10-27-38 4-24-39 6- 2-39	4 3 2 4 0.5 5 2	37	27.8      12- 8-37 to 6- 5-39	June 1938 Nov. 1938 Jan. 1939 Apr. 1939	+ + 0 +	Recent infection, fall of 1936, from tuberculous roommate. Development of lesion with subsequent extension five months after infection. Recent films, May 1939, show no extension since Oct. 1938.
13 Stef. 88261 21 M.	9-25-35 to 6- 1-39 Wt. Gain 4 lb.	10-25-35 12- 4-36 4- 7-37 6- 6-37 8-31-37 11-29-37 1- 3-38 4-14-38 1-30-39 5-11-39	4.5 4 4 7 13* 4.5 3 3 9 7	116	22.7      12-15-36 to 6- 1-39	Dec. 1936 Feb. 1937 Apr. 1937 May 1937 Jan. 1938 May 1938 Feb. 1939	+ + + 0 + + +	Interlobar fibrotic band noted on right in Sept. 1935. Subsequently small lesions noted in left clavicular region and above band on rt. Rest treatment with retrogression. Subsequent minimal extension in the right apex. Process active for five years without production of symptoms. Entered Sanatorium June 1939.
14 Holm 88578 20 M.	9-27-35 to 6- 8-39 Wt. Gain 20 lb.	3-21-36 2-26-37 5-27-37 10-22-37 2-10-38 10-24-38 5-18-39	2 2.5 3 5 3 1 2	28	9.8      3-21-36 to 6- 8-39	Mar. 1936 Mar. 1938 Mar. 1939	0 0 0	Soft minimal left subclavicular infiltrate first noted Sept. 1935. Subsequent retrogression with fibrosis and development of 6 mm. calcification.
15 McClell 89973 19 M.A.	9-23-35 to 5- 5-39 Wt. Loss 6 lb.	10- 8-35 1-27-36 9-15-36 1-17-37 5-17-37 10- 4-37 2-21-38 10- 3-38 5- 4-39	11 10 10 6 11 15 10 2 25	48	46.4      1-30-37 to 5- 4-39	May 1937 Oct. 1937 Mar. 1938 May 1938 Oct. 1938 May 1939	+ + 0 + + +	Lesion intermittently but inadequately treated since 1935. No apparent change in films from 1935 to Feb. 1939. Extension with small cavitation Feb. to May 1939.

## SUBCLINICAL PULMONARY TUBERCULOSIS

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TABLE I—Continued

Case Age	Period of Observation Weight	Blood Sedi-mentation Rate		Leukocyte Reaction		Gastric Aspiration with Pig Inoculation		Roentgen-Ray Study
		Date	Rate	No.	Ave. Medlar Index	Date	Result	
16 Koltun 91862 19 M.	9-18-36 to 5-25-39 Wt. Gain 7 lb.	11-22-37 10-14-38 1-28-39 4-28-39 Average	15 3 4 6 7	24	21.3	Nov. 1937 Jan. 1939	0 0	Contact tuberculous uncle 1932. Pleural effusion 1933. Film Sept. 1936 negative. Fluoroscopic Nov. 1937 showed small infiltrate. San. treatment 9 months. Films Oct. 1938 and June 1939 show continued re- gression.
17 Tite 93081 18 Hilum tbc.	9-24-36 to 5-16-38 Wt. Gain 22 lb.	3-11-37 3-22-37 4-1-37 11-29-37 1-15-38 3-22-38 5-16-38 Average	23 9 8.5 5 4 5 4 8.3	16	17.9	Mar. 1937 Dec. 1937 Mar. 1938	++ ++ ++	Negative film Sept. 1936. Massive pleural effusion March 1937. Subsequent involvement of right hilum glands but with no visible parenchymal change. No recent films but patient writes—July 1939—that he is well and working.
18 Suku 93257 23 M.	10-2-36 to 6-7-39 Wt. Gain 10 lb.	10-22-36 2-1-37 6-11-37 10-11-37 3-22-37 6-9-39 Average	4 8 9 7 11 2.5 6.4	46	44.6	Nov. 1936 Feb. 1937 Mar. 1938 Apr. 1939	++ ++ ++ 0	Contact with tuberculous room-mate summer 1936. Soft lesion 22 X 24 mm. noted in left clavicular region Oct. 1936. Serial films since have shown complete resolution of the in-filtrate.—June 1939.
19 Kub 93502 20 M.	9-25-36 to 4-27-37 Wt. Stat.	11-4-36 12-9-36 4-27-37 Average	9 7 3.5 6.5	10	39.4	Nov. 1936	0	Soft infiltrate first noted in left apex Oct. 1936. Subsequent extension apparent in Feb. 1937. No further change to June 1937. Failed to return to school. Recent film, 1939, shows retrogression of lesion.
20 Marv. 93631 22 M.	9-26-36 to 7-7-39 Wt. Gain 7 lb.	10-26-36 12-16-36 1-25-37 6-8-37 11-5-37 4-23-38 5-18-39 Average	3 8 2 6 3 3 4 3.2	50	32.6	Oct. 1936 Nov. 1937 Apr. 1938 May 1939	++ ++ ++ 0	Soft infiltrate first noted rt. apex Oct. 1936. Subsequent extension Jan. to June 1937. Retrogression noted Nov. 1937. Extension again in April 1938. Retrogression since that time with little residual evidence of infiltrate.—July 1939.
21 Fried 94383 17 M.A.	9-19-36 to 6-2-38 Wt. Stat.	10-14-36 12-2-36 5-1-37 11-2-37 3-19-38 Average	6 7 6.5 9 3 6.3	51	26.8	Oct. 1936 Nov. 1937 Mar. 1938	++ ++ ++	Former San. patient, considered cured. During interval Sept. 1936 to May 1938 both retrogression and extension of small infiltrates in the clavicular areas were noted. Letter June 1939 indicates patient still clinically well.
22 Boncyk 93719 18 M.	9-26-36 to 6-10-39 Wt. Gain 12 lb.	10-16-36 1-20-37 1-27-37 5-25-38 10-18-38 1-10-39 3-22-39 Average	5 11 6.5 3 1 3 7 6.3	33	16.2	Jan. 1937 Dec. 1937 Feb. 1938 June 1938 Oct. 1939 Jan. 1939 Mar. 1939	0 ++ ++ ++ ++ ++ ++ 0	Former San. patient. Small lesion left apex Sept. 1936 with extension noted Nov. 1937. Frcc bacilli in stomach. Pneumothorax instituted June 1938. Marked retrogression of lesion June 1939.
23 Hard 94875 20 M.	9-22-36 to 6-4-38 Wt. Stat.	10-13-36 11-23-36 3-11-37 6-11-37 10-7-37 6-3-38 Average	7 5 9 8 5 4 6.3	29	29.2	Oct. 1936 Feb. 1937 Feb. 1938	0 0 0	Two small infiltrates 12 X 18 and 10 X 12 mm. noted in right subclavicular region Sept. 1936. Subsequent gradual resorption with only fibrotic strands remaining June 1938.

TABLE I—Continued

Case Age	Period of Observation Weight	Blood Sedimentation Rate		Leukocyte Reaction		Gastric Aspiration with Pig Inoculation		Roentgen-Ray Study
		Date	Rate	No.	Ave. Medlar Index	Date	Result	
24 · Mart 94935 19 M.	9-22-36 to 12-13-38 Wt. Gain 7 lb.	10-19-36	8.5	33	21.6	Oct. 1936 Mar. 1938 Oct. 1938	0	Scattered small infiltrates in right apex and clavicular region first noted Oct. 1936. Extension in Oct. 1937 with subsequent marked retrogression and fibrosis of lesion Oct. 1938.
		3-16-37	11				0	
		4-30-37	6.5				0	
		6-10-37	7					
		10-4-37	10					
		3-16-38	8					
		10-5-38	3.5		10-19-36 to 10-13-39			
		Average	7.8					
25 Merk 95004 22 M.	9-22-36 to 5-31-39 Wt. Stat.	6-10-38	4	23	17.7	June 1938 Sept. 1938 Dec. 1938 June 1939	0	Recent infection with development of visible progressive tuberculosis limited to apical pleura and a 5 × 5 mm. density in the right clavicular region.
		9-1-38	4				+	
		12-2-38	6.5				0	
		3-24-39	7				0	
		6-6-39	8.5					
		Average	6.		10-13-38 to 5-31-39			
26 Gust 95466 29 M.	2-18-37 to 3-23-39 Wt. Gain 4 lb.	3-1-37	12	29	33.9	Mar. 1937 May 1937 Oct. 1937 Feb. 1938 Nov. 1938 Mar. 1939	+	Films taken at 4 month intervals from Feb. 1937 to March 1939 show minimal apical lesions undergoing both slight progression and retrogression.
		5-11-37	9				+	
		10-4-37	6				+	
		2-18-38	8				+	
		5-11-38	9				+	
		3-23-39	7				+	
		6-3-39	9		10-7-37 to 6-1-38			
		Average	7.6					
27 Kilb 97740 17 M.	9-16-47 to 5-29-39 Wt. Gain 13 lb.	10-15-37	5	45	18.8	Oct. 1937 Apr. 1938 Nov. 1938 Mar. 1939	0	Oval 15 × 22 mm. density right subclavicular area noted in Sept. 1937. Retrogression at original site with extension at the periphery May 1939.
		12-18-37	5				+	
		3-10-38	2				+	
		6-7-38	2.5				+	
		10-14-38	1				0	
		5-31-39	2.5		10-14-37 to 5-16-39			
		Average	3					
28 Gleb 98167 23 M.	9-18-37 to 6-5-38 Wt. Gain 20 lb.	2-8-39	0.5	16	32	Feb. 1939 May 1939	+	Film Sept. 1937 showed thickened pleura at the left base, and calcified deposits in both lungs. No change to May 1938. In Feb. 1939 soft infiltrate in right clavicular area noted. Film May 1939 showed marked retrogression. Free bacilli persist.
		5-5-39	2				+	
		5-24-39	2					
		Average	1.5					
					2-8-39 to 6-5-39			
29 Elson 98179 23 M.	9-18-37 to 5-5-39 Wt. Gain 9 lb.	10-7-37	10	18	35.6	Nov. 1937 May 1938	0	Small infiltration left clavicular region first noted Sept. 1937. Retrogression of lesion from Sept. 1937 to June 1938. Further retrogression noted June 1939.
		3-11-38	4				0	
		6-3-38	6					
		4-29-39	5					
		Average	6.3		10-7-37 to 6-3-38			
30 Thad 98202 18 M. to M.A.	9-18-37 to 2-6-39 Wt. Stat.	10-11-37	5.3	27	25	Oct. 1937 Oct. 1938	+	San. treatment 1935 to 1937. Apical infiltrates noted on enrollment Sept. 1937. Readmitted to San. Feb. to Aug. 1938. Re-enrolled Sept. 1938 with no apparent change in lesion. In Jan. 1939 developed tbc. in left wrist and cavity at apex of lung. Returned to Sanatorium.
		12-10-37	8				0	
		9-30-38	4					
		2-6-39	4					
		Average	5.4		10-11-37 to 2-6-39			
31 Beck 98356 22 M.	9-20-37 to 6-7-39 Wt. Gain 12 lb.	12-13-38	4.5	23	16.3	Dec. 1938 Apr. 1939	+	Film Sept. 1937 negative. Dec. 1938 soft lesion found in left subclavicular region. Subsequent films Jan. 1939 to June 1939 showed marked resorption of lesion.
		4-15-39	5				0	
		6-1-39	7					
		Average	5.2		12-13-38 to 6-7-39			

TABLE I—Continued

Case Age	Period of Observation Weight	Blood Sedi- mentation Rate		Leukocyte Reaction		Gastric Aspiration with Pig Inoculation		Roentgen-Ray Study
		Date	Rate	No.	Ave. Medlar Index	Date	Result	
32 Loch 100459 22 M.	11-17-37 to 6-16-39 Wt. Gain 14 lb.	1-13-38 3- 3-38 6- 2-38 10-12-38 5- 5-39 Average	8.5 6 2 0.5 3 4	25	25.4  Average index before pneu- mothorax 23.3 After pneumo- thorax 27.9. 1-12-38 to 5-31-39	Jan. 1938 Oct. 1938 May 1939	+ 0 0	Film of Nov. 1937 showed soft 18 X 22 mm. lesion in right clavicular region. Cavity noted Mar. 1938 which became larger in June 1938. Pneumothorax instituted in July 1938. Cavi- ty closed Oct. 1938. Films of June 1939 show residual 6 by 9 mm. lesion.
33 Cast 101659 21 M.	9-16-38 to 6- 3-39 Wt. Stat.	10- 6-38 12- 6-38 3- 1-39 5-16-39 Average	5 6 13* 11† 11.2	17	30.8  10- 6-38 to 5- 9-39	Oct. 1938 Mar. 1939	0 0	Small infiltrates both apices and in right subclavicular re- gion. Calcium in rt. lung and hilum glands. From Sept. 1938 to June 1939 definite re- trogression in subclavicular lesion. No change in calcium or at apices.
34 Rye 102038 21 M.	9-19-38 to 6-10-39 Wt. Gain 8 lb.	10- 7-38 1-12-39 4- 4-39 5-19-39 Average	4 5.5 5 10.5 6.3	19	35.6  10- 7-38 to 5-23-39	Oct. 1938 Apr. 1939	0 +	Soft infiltrate in right apex noted Sept. 1938. No change in serial films including those of June 1939.
35 Hony 102507 26 M.A.	9-22-38 to 5-24-39 Wt. Stat.	10-11-38 2-25-39 4-27-39 5-24-39 Average	8 15 9 12 9.8	24	14.9  10-11-38 to 5-24-39	Oct. 1938 Mar. 1939	+ +	Sanatorium patient 1930-1937. Discharged apparently cured. Enrolled Sept. 1938. Several old lesions upper half of left lung which showed intermittent change to June 1939. Note good leukocyte response.
36 Hig 102871 17 M.	9-15-38 to 6- 9-39 Wt. Gain 6 lb.	11- 1-38 5-23-39 Average	1 4 2.5	20	44.3  11- 1-38 to 5-18-39	Nov. 1938 May 1939	0 Re- fused test	Small infiltrate with 3 mm. cavi- ty noted Sept. 1938 in right clavicular area. Serial films to June 1939 show retrogression with closure of cavity.
37 Gil 103748 21 M.	9-19-38 to 2- 1-39 Wt. Gain 10 lb.	10-20-38 1-11-39 2- 1-39 Average	3 6 5.5 4.8	9	21.6  10-20-38 to 2- 1-39	Oct. 1938	+	Small soft lesion noted in left apex Sept. 1938. Slight ex- tension occurred prior and sub- sequent to San. treatment Feb. 1939. Pneumothorax instituted April 1939.
38 Smy 104278 18 M.	8-20-38 to 6- 8-39 Wt. Gain 8 lb.	12- 9-38 5- 4-39 Average	9 5 7	16	25.3  12- 8-38 to 6- 8-39	Nov. 1938 Feb. 1939 June 1939	+ 0 0	Small infiltrate right clavicular region noted Sept. 1938. No change in appearance to June 1939.
39 Swi 104571 18 M.	9-21-38 to 6-12-39 Wt. Gain 3 lb.	10-21-38 1-11-39 6-12-39 Average	1 3 5 3	17	24.2  2- 3-39 to 6-12-39	Oct. 1938 Jan. 1939 Apr. 1939	+ + 0	Soft infiltrate right clavicular region noted Sept. 1938 with subsequent marked retrogres- sion of lesion to July 1939.
40 DrE 27 M.	2-10-37 to 5-29-39 Wt. Stat.	2-12-37 3- 1-37 1- 9-38 6-28-39 Average	2 3 5 5 3.8	29	14.3  1-20-37 to 5-29-39	Feb. 1937 Mar. 1938 Nov. 1938	not done 0 0	Films of Jan. 1936 negative. Bilateral small apical infiltrates Feb. 1937 with subsequent complete resolution of lesion June 1939.

\* Ear infection.

† Acute respiratory infection.



Cover glass smears were made for the differential count by touching a clean 22 mm. cover glass (soaked in concentrated nitric acid, washed successively in water, soap solution, water, and stored in 95 per cent alcohol until they were wiped dry at the time of the count), to a small drop of blood from the ear puncture, being careful not to touch the ear. Another cover glass was placed diagonally on this, and the two pulled apart just before the blood stopped spreading. An even smear is obtained in this way, the thickness of which can easily be varied. The smears were stained with Wright's stain (National Aniline Dye and Chemical Co., New York), and three smears, mounted on a slide with immersion oil, were covered as completely as possible.

The percentages of monocytes, neutrophiles, small lymphocytes, large lymphocytes, young lymphocytes, eosinophiles, and basophiles reported were based on the 400 leukocytes counted for each sample. All mononuclear cells with granular, muddy blue cytoplasm were considered monocytes, regardless of the shape of the nucleus. No effort was made to differentiate between filamented and non-filamented neutrophiles, but large lymphocytes were distinguished from small lymphocytes by their size, being about the size of neutrophiles in the same or nearby fields. Young lymphocytes were distinguished by their very blue cytoplasm, and, usually accompanying this, their larger size and lighter-staining nuclei. Occasionally a cell of relatively large size was found which had very blue cytoplasm and light-staining nucleus sometimes containing still lighter areas (nucleoli); these were reported as "large young cells," since they were too young to determine their origin.

#### INTERPRETATION OF DATA

The fact is appreciated that it is hazardous to interpret laboratory data concerned with a pathological process which has not yet completed its usual long chronic course. For absolute accuracy, interpretation should be deferred until the process is completely healed (a practical impossibility) or until the patient has died from the disease. Since the ideal is impossible it is nevertheless important and valuable to study the course of the pathologic process during a "period of the disease."

A favorable clinical course, as indicated by a gain in bodily weight (table 2), absence of fever, and a general feeling of well being, though desirable, should not be the basis for judging the patient's progress. Weight loss, however, should be considered with concern. In the one individual of this series who lost weight the tuberculous process was progressive. Judgment based on a favorable clinical course, rather than on critical laboratory study and consideration of the underlying pathology, offers an adequate explanation of the frequent so-called "breakdowns" and "recurrences." These unfortunate occurrences represent in most instances extensions of active tuberculous foci which have never healed. Insurance companies, penalized by poor risks, appreciate more than physicians the frequency and seriousness of recurrences among the apparently cured. Their judgment is based on eventualities, and "clinical benignity" and "apparently cured," though suggestive at close range of satisfactory progress, have not proved to be sufficient or positive evidence of real cure. To protect themselves, underwriters have found that the elapse of sufficient time is their best practical guide in determining that tuberculosis is "sufficiently cured" to warrant the risk of contract.

TABLE II  
Correlation of Laboratory Methods

Case No.	Weight Pounds	Erythrocyte Sedimentation Rate	Leukocyte Reaction	Guinea Pig Gastric Content	Roentgen-Ray*
1	0	Normal	Unfavorable	+	N.C.
2	0	N.	Favorable	+	R.
3	+29	N.	Fav.	+	R.
4	+16	N.	Unf.	+	R.
5	+11	Inc.	Equivocal	+	E.
6	+23	Inc.	Unf.	+	E.
7	+24	N.	Fav.	+ to -	E.
8	+14	N.	Eq.	+ to -	R.
9	+16	N.	Eq.	+	E.
10	+25	N.	Fav.	+	R.
11	+20	N.	Unf.	0	R.
12	+13	N.	Eq.	+	E.
13	+ 4	N.	Eq.	+	E.
14	+20	N.	Fav.	0	R.
15	- 6	Inc.	Unf.	+	E.
16	+27	N.	Eq.	0	R.
17	+22	N.	Fav.	+	E.
18	+10	N.	Unf.	+ to -	R.
19	0	N.	Unf.	0	E.
20	+ 7	N.	Unf.	+ to -	R.
21	0	N.	Eq.	+	E.
22	+12	N.	Fav.	+ to -	R.
23	0	N.	Eq.	0	R.
24	+ 7	N.	Eq.	0	R.
25	0	N.	Fav.	+ to -	E.
26	+ 4	N.	Unf.	+	E.
27	+13	N.	Fav.	+ to -	R.
28	+20	N.	Unf.	+	R.
29	+ 9	N.	Unf.	0	R.
30	0	N.	Eq.	+ to -	E.
31	+12	N.	Fav.	+ to -	R.
32	+14	N.	Eq.	+ so -	R.
33	0	Inc.	Unf.	0	R.
34	+ 8	N.	Unf.	+	N.C.
35	0	N.	Fav.	+	E.
36	+ 6	N.	Unf.	0	R.
37	+10	N.	Eq.	+	E.
38	+ 8	N.	Eq.	+ to -	N.C.
39	+ 3	N.	Eq.	+ to -	R.
40	0	N.	Fav.	0	R.
Totals	Gain 407 Loss 6	N 36 I 4 90% 10%	F 12 U 14 E 14 30% 35% 35%	P 18 P to N 12 N 10 45% 30% 25%	R 22 E 15 N 3 55% 37.5% 7.5%

\* R.—Regression; E.—Extension; N.C.—No change.

Since the erythrocyte sedimentation rate was normal in 36 of 40 or 90 per cent of the active cases, the test, when normal, is of limited value as an aid in determining the status of the subclinical lesion. It offers little of the assurance, so generally accepted in the past, that the lesion is either benign or inactive. As indicated in table 3, the course of the lesion in the small group (10 per cent) having an increase in rate was less favorable than in those with a normal response.

TABLE III  
Erythrocyte Sedimentation Rate  
Forty Cases

Normal	% of Cases	Roentgen-Ray		
36	90%	Retrogression	21	58.3%
		Extension	12	33.3%
		No change	3	8.3%
Increase		Roentgen-Ray		
4	10%	Extension	3	75.0%
		Retrogression	1	25.0%

In interpreting the leukocyte response, as shown in tables 2 and 4, the cases have been arbitrarily divided into three groups: those showing a favorable leukocytic index with an average index below 20; those with an unfavorable index, above 30; and the equivocal group in which the index falls between 21 and 30.

Those with indices between 21 and 30 are considered equivocal because normal healthy individuals with negative Mantoux tests and normal chest roentgenograms may fall in this group. Two such students volunteering to report for a weekly blood count for a period of three and six months were found to have an average leukocytic index of 22 and 29 respectively. Medlar,<sup>14</sup> in studying the leukocytic reaction in normal individuals, found that in 113 or 24 per cent of the 478 counts done, the average index registered between 21 and 30.

TABLE IV  
Leukocyte Reaction  
Forty Cases

Favorable	% of Cases	Roentgen-Ray		
12	30%	Retrogression	9	75%
		Extension	3	25%
Unfavorable		Roentgen-Ray		
14	35%	Retrogression	8	57.2%
		Extension	5	35.7%
		No change	1	7.1%
Equivocal		Roentgen-Ray		
14	35%	Extension	7	50.0%
		Retrogression	6	42.9%
		No change	1	7.1%
Unfav. + Equiv.		Roentgen-Ray		
28	70%	Retrogression	15	53.6%
		Extension	11	39.3%
		No change	1	7.1%

In table 4 the leukocyte reactions are compared with the progress of the lesion as determined by the roentgenogram. In the favorable leukocytic index group, 9 of 12, or 75 per cent of the cases, showed retrogression of the lesion. In two of the three cases withdrawing from school because of initial

extension, but with favorable leukocyte reactions, the subsequent pathological course of the lesion was favorable. Both slight extension and retrogression occurred in the third case in this group in which the leukocyte count was favorable. This patient (Case 35) had received sanatorium care for seven years and was considered cured. She is clinically well, but her gastric contents are positive. The favorable leukocyte reaction, barring a pathological accident, probably offers some assurance that, though the lesion is active, there is little danger of rapid extension. From these data it appears that a favorable leukocyte reaction may be reliably accepted as indicating that the pathological process is healing, or, as in the exceptional case, the process is being controlled. In no instance where the total number of lymphocytes or the lymphocyte percentage was high has the pathological process taken a significantly unfavorable course.

An unfavorable leukocyte reaction (table 4), however, does not necessarily mean an unfavorable prognosis, for in 14 cases classified as having unfavorable leukocyte reactions, retrogression occurred in 8, or 57.2 per cent. Two of these eight had high and ominous leukocytic indices. Case 18, with an average leukocytic index of 44.6 showed complete resolution of the infiltrate. Case 11, with an average leukocytic index of 62.9 also showed retrogression of the lesion, and though no recent roentgenogram of the lungs is available, information from the patient's father indicates that if extension has occurred, it has not been sufficient to interfere with his marriage or health. Objection to presentation of this case may be made on the basis that proof that the lesion is tuberculous is not at hand since the gastric contents were always negative. The roentgen-ray appearance and site of the lesion, however, favor the diagnosis of tuberculosis (figure 1).

In the group of 14 cases with equivocal leukocytic reactions, the results approximated those of the unfavorable group. Combining the equivocal and unfavorable groups, table 4, no significant changes in the figures occur. Since retrogression of the lesion occurred in 53 per cent of the combined unfavorable and equivocal groups, an unfavorable or questionable unfavorable leukocyte reaction *does not portend, in the majority of subclinical cases, the predicted unfavorable course.*

The weekly blood counts of five cases are presented (table 5). Numbers 1 and 2, representing Cases 2 and 14, indicate a satisfactory lymphocyte response which, when present, indicates, with few exceptions, a favorable prognosis. Number 3, representing Case 18, is presented to show that the absence of a good lymphocyte response does not necessarily indicate an unfavorable course, for in this instance complete resolution of the infiltrate occurred.

Number 4, representing Case 6, shows a very bizarre leukocyte reaction for a period of three weeks, during which time and subsequent thereto an extension of the lesion occurred. The patient was without symptoms, and though the count suggested an acute mononucleosis, the fatigue and adenopathy accompanying that condition were absent. On one occasion the per

cent and total number of monocytes were higher than the per cent and total number of either the lymphocytes or neutrophils. The details in each case are given in table 1.

Number 5, representing Case 12, is of especial interest since it represents the leukocyte reaction following known infection, with the subsequent development of an active lesion. The lesion reached its maximum extent in October 1938, since which time there has been some retrogression. The leukocyte reaction might be interpreted as unfavorable though during recent months there has occurred no further extension of the process.

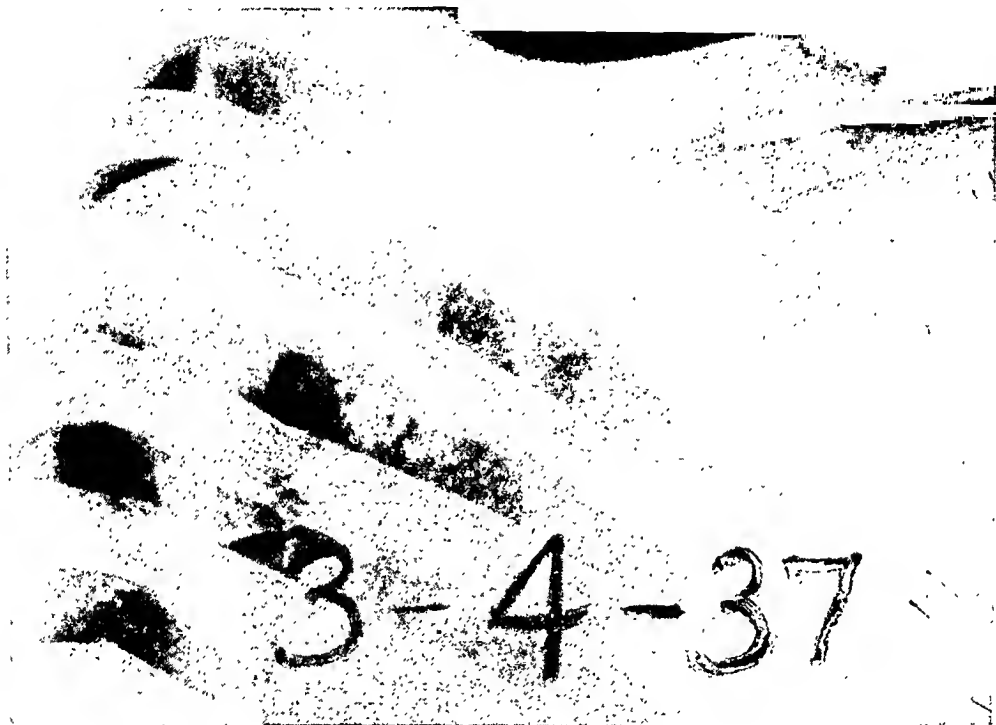


FIG. 1. Apical infiltration in Case 11.

This particular case raises the question of the benignity of first infection tuberculosis. If we accept the formerly negative Mantoux test as evidence of the absence of previous infection, this case represents a progressive pathological process resulting from the first infection. The subsequent course of this particular lesion cannot be foretold, but if its course follows that of five other similar cases, progression of the lesion may be anticipated. That the first infection is usually benign is substantiated by the large number of infected individuals who fail to develop progressive tuberculosis, but the statement that tuberculosis resulting from first infection is always benign<sup>15</sup> and that treatment has no influence on the primary complex should be accepted as an opinion rather than as a fact. Quoting Myers<sup>16</sup> in his recent article: "It is now known that treatment has no influence on this primary complex, as the walls form around the bacilli in the same way when the per-

TABLE V

## Weekly Blood Counts in Five Patients

Case 2. Favorable leukocyte reaction with subsequent marked retrogression of lesion.

Leukocyte Reaction No. 1								
Date	Total	M	%	L	%	N	%	Index
10-14-38	12,000	810	6.8	3780	31.5	6570	54.8	19
10-21-38	11,150	1422	12.8	3512	31.5	5268	47.3	16
10-28-38	10,950	685	6.3	3680	33.5	5900	53.8	14
11- 4-38	9,650	773	8.0	2510	26.0	6050	62.8	24
11-11-38	10,200	485	4.8	3140	30.8	5950	58.3	18
11-18-38	9,550	980	10.3	2720	28.5	5300	55.5	19
11-25-38	11,650	905	7.8	3180	27.3	7300	60.3	25
12- 2-38	10,300	900	8.8	2630	25.5	6450	62.3	24
12- 9-38	10,500	710	6.8	2970	29.3	6460	61.5	22
12-16-38	7,350	625	8.5	2460	33.5	3725	51.0	11
1- 6-39	11,500	720	6.3	4025	35.0	6300	54.8	11
1-13-39	10,350	905	8.8	3390	32.8	5775	55.8	14

Case 14. Favorable leukocyte response with healing by fibrosis and calcification.

Leukocyte Reaction No. 2								
Date	Total	M	%	L	%	N	%	Index
2-26-37	8,875	666	7.5	3239	36.5	4770	53.8	10
3-31-37	9,750	878	9.0	4217	43.3	4509	46.3	1
4- 7-37	8,225	576	7.0	3208	39.0	4277	52.0	7
4-14-37	8,075	404	5.0	2342	29.0	5208	64.5	22
4-28-37	10,175	763	7.5	4833	47.5	4579	45.0	0
5-27-37	8,200	820	10.0	2624	35.8	4346	53.0	9
6- 3-37	7,725	521	6.8	2839	36.8	4172	53.0	9
10-22-37	7,275	455	6.3	2474	34.0	4165	57.3	13
11-11-37	8,100	324	4.0	2633	32.5	5063	62.5	19
12- 2-37	7,050	159	2.3	2362	33.5	4442	63.0	17
12- 6-37	7,750	388	5.0	3790	36.0	4427	57.3	11
1-14-38	7,450	298	4.0	2924	39.3	4060	54.5	8
2-10-38	7,550	504	6.5	2790	36.0	4340	56.0	11
3-24-38	10,400	754	7.3	4004	38.5	5382	51.8	8
6-17-38	8,500	489	5.8	2465	29.0	5355	63.0	22
10-24-38	9,200	875	9.5	3295	35.8	4925	53.5	10
10-31-38	8,150	510	6.3	2820	34.5	4590	56.3	12
11-23-38	8,200	555	6.8	3260	39.8	4260	52.0	6
12- 5-38	7,800	370	4.8	3320	42.5	4055	52.0	4
12-12-38	8,050	362	4.5	2920	36.3	4670	58.0	12
1- 9-39	7,850	432	5.5	3560	45.3	3750	47.8	1
5- 2-39	8,750	438	5.0	3760	43.0	4375	50.0	3
5-18-39	7,000	385	5.5	2625	37.5	3880	55.5	9
5-26-39	7,850	392	5.0	3140	40.0	4300	54.8	8
6- 8-39	8,000	640	8.0	3140	39.3	4050	50.5	6

Table 6 continued on page 2300.

son goes about the usual activities of life as when he is placed on strict bed rest or collapse therapy. Nothing destroys the tubercle bacilli or reduces the allergy of the tissues. Apparently nothing has any influence on the later escape of bacilli from the primary foci. The infant or child with primary tuberculosis on treatment, including strict bed rest, may have meningitis,

TABLE V—*Continued*

Case 18. Continued unfavorable leukocyte response with complete resolution of infiltrate.

## Leukocyte Reaction No. 3

Date	Total	M	%	L	%	N	%	Index
2-22-37	8,625	647	7.5	1423	16.5	6339	73.5	44
2-24-37	5,850	351	6.0	1053	18.0	4285	73.3	41
2-26-37	7,400	574	7.8	1628	22.0	5051	68.3	31
3- 1-37	8,225	802	9.8	1193	14.5	5922	72.0	49
3- 3-37	9,000	585	6.5	1328	14.8	6908	76.8	51
3- 8-37	8,700	653	7.5	1523	17.5	6375	73.5	42
3-10-37	10,275	1361	13.3	1541	15.0	7115	69.3	45
3-17-37	10,400	598	5.8	1846	17.8	7748	74.5	42
3-22-37	9,875	617	6.3	1778	18.0	7158	73.5	42
3-24-37	10,875	924	8.5	2420	22.3	7395	68.0	31
3-29-37	11,900	1160	9.8	1785	15.0	8747	73.5	52
3-31-37	10,325	800	7.8	1368	13.3	8028	77.8	60
4- 2-37	10,875	1006	9.3	2066	19.0	7640	70.3	37
4- 5-37	8,075	626	7.8	1211	15.0	5976	74.0	49
4- 7-37	8,575	493	5.6	1544	18.0	6367	74.3	41
4-14-37	10,650	639	6.0	1331	12.5	8334	78.3	62
4-19-37	9,850	345	3.5	1084	11.0	8225	83.5	76
4-21-37	10,150	1066	10.5	1573	15.5	7232	71.3	45
4-26-37	11,100	805	7.3	1776	16.0	8297	74.8	43
5- 3-37	8,500	510	6.0	1404	16.8	6375	75.0	44
5- 5-37	12,050	452	3.8	1808	15.0	9555	79.3	56
5-10-37	9,125	662	7.3	1620	17.8	6684	73.3	41
5-12-37	8,525	171	2.0	1684	19.8	6479	76.0	38
5-17-37	8,200	472	5.8	1538	18.8	6068	74.0	39
5-19-37	10,300	798	7.8	1004	9.8	8389	81.5	100
5-26-37	10,450	810	7.8	1541	14.8	7890	75.5	50
6- 2-37	10,550	633	6.0	1583	15.0	8071	76.5	50
6- 7-37	10,875	625	5.8	1822	16.8	8211	75.5	44
10-11-37	8,875	600	6.8	1376	15.5	6678	75.3	48
10-18-37	7,875	295	3.8	1831	23.3	5453	69.3	30
10-25-37	8,375	628	7.5	1591	19.0	6009	71.8	38
11- 1-37	8,975	292	3.3	2064	23.0	6440	71.8	31
11- 8-37	9,575	527	5.5	2801	29.3	6080	63.5	22
11-15-37	10,350	492	4.8	2044	19.8	7633	73.8	37
11-22-37	8,700	370	4.3	1805	20.8	6416	73.8	35
11-29-37	9,450	732	7.8	1654	17.5	6851	72.5	41
12- 6-37	11,200	476	4.3	2268	20.1	8176	73.0	39
12-13-37	10,050	276	2.8	2286	22.8	7186	71.5	31
1-10-38	7,750	407	5.3	1647	21.3	5464	70.5	33
1-17-38	8,850	575	6.5	1859	21.0	6217	70.3	33
3- 7-38	8,000	460	5.8	1740	21.8	5600	70.0	32
3-14-38	11,250	618	5.5	1630	14.5	8800	78.3	56
3-21-38	8,450	696	8.3	2050	24.3	5510	65.3	27
4- 4-38	8,800	485	5.5	1650	18.8	6470	73.5	39

Table 5 continued on page 2301

miliary tuberculosis or tuberculous pneumonia as readily as the one leading an active life. Moreover, the person who has had drastic treatment for the primary complex apparently is just as likely to fall ill later from acute or chronic forms of the disease as the person who has had no treatment for the primary disease."

Critical analysis of the statements made in the above paragraph necessitates careful consideration as to whether sufficient evidence is at hand to

TABLE V—*Continued*

Case 6. Extension of infiltrate during time of bizarre leukocytic reaction with high monocyte and lymphocyte counts, and low neutrophile count.

## Leukocyte Reaction No. 4

Date	Total	M	%	L	%	N	%
3- 3-37	9,800	785	8.3	1789	18.3	6958	71.0
3-10-37	8,975	494	5.5	1817	20.3	6484	72.3
3-17-37	4,025	523	13.0	1228	30.5	2073	51.5
3-24-37	6,650	2261	34.0	1895	28.5	2394	36.0
3-31-37	7,150	2860	40.0	2234	31.3	1913	26.8
4- 7-37	5,600	1582	28.3	2198	39.3	1638	29.3
4-12-37	7,150	483	6.8	2467	34.5	3950	55.3
4-28-37	8,575	579	6.0	2165	25.3	5724	66.8
5- 6-37	7,225	415	5.8	1969	27.3	4606	63.8
5-13-37	8,175	715	8.8	2248	27.5	5089	62.3
5-20-37	8,250	660	8.0	1588	19.3	5940	72.0
5-27-37	9,450	756	8.0	2032	21.5	6591	69.8
6- 3-37	9,000	810	9.0	2160	24.0	5670	63.0
6- 8-37	9,325	909	9.8	2448	26.3	5665	60.8

*Table 5 continued on page 2302.*

justify such conclusions. The fact that a large majority of first infection lesions heal does not justify the conclusion that a similar course occurs in all such lesions. Doubt exists as to whether we can actually determine that a process is no longer pathologically active. Accepted evidence (no change in serial roentgenograms) that a lesion is healed has been proved to be erroneous. This error is suggested in Myers' discussion when he mentions "escape of bacilli from primary foci," and again when he says: "The infant or child with primary tuberculosis on treatment, including strict bed rest (no exogenous reinfection possible) may have meningitis, miliary tuberculosis or tuberculosis pneumonia as readily as the one leading an active life." A lesion with these potentialities can hardly be considered benign. Many will question whether adequate evidence is available to justify the conclusion that treatment of the primary complex is without influence on the process. Tubercle formation with destruction of normal tissue occurs in both first infection and reinfection tuberculosis and though usually not progressive in either case, it appears both inconsistent and invalid that the same pathological process should be seriously considered and treated in the second instance and not in the first. Furthermore, without proof of when infection occurred, distinction between lesions resulting from first infection or reinfection is frequently not possible and should not be attempted.

At present, by observation of the early subclinical lesion, evidence is accumulating that, in a small percentage of cases, the pathologic process resulting from the first infection never completely heals, though for years there may be no indication of its activity other than the occasional presence of tubercle bacilli in the gastric contents as determined by guinea pig inoculation. Potentially, such a lesion is always a menace, although it is often erroneously



TABLE V—*Continued*

Case 12. Patient infected fall of 1937 by tuberculous room-mate. Mantoux formerly negative became positive and visible tuberculous lesion was first noted in March 1938. The above counts represent his leukocyte response since infection. Films showed extension until January 1939, since which time some resolution has occurred. Gastric contents positive, patient never ill, no fever, weight gain 13 lb. Count may be considered either equivocal or unfavorable.

## Leukocyte Reaction No. 5

Date	Total	M	%	L	%	N	%	Index
12- 8-37	7,600	703	9.3	2109	27.8	4427	58.3	21
12-15-37	8,450	613	7.3	1838	21.8	5746	68.0	31
3-10-38	7,600	589	7.8	1720	22.5	5110	67.3	30
3-30-38	10,100	960	9.5	2145	21.3	6895	68.3	32
4- 6-38	8,600	881	10.3	2625	30.5	4900	58.0	18
4-13-38	7,850	765	9.8	2415	30.8	4530	57.8	17
5- 4-38	8,150	590	7.3	1510	18.5	5960	73.3	40
5-11-38	9,450	755	8.0	1654	17.5	6875	72.8	42
5-18-38	8,450	655	7.8	1920	22.8	5700	67.5	29
5-25-38	10,250	769	7.5	1820	17.8	7100	69.3	39
6- 1-38	8,800	462	5.3	1670	19.0	6360	72.3	38
6- 9-38	11,350	965	8.5	1985	17.5	8370	73.8	42
10-13-38	6,400	416	6.5	2016	31.5	3648	57.0	16
10-27-38	7,000	630	9.0	2020	28.8	4100	58.5	20
11- 3-38	8,500	553	6.5	1660	19.5	6100	71.8	37
11-10-38	9,050	595	6.5	2680	29.3	5600	61.3	21
11-17-38	6,950	730	10.5	2040	29.3	4050	58.3	20
12- 1-38	8,950	715	8.0	2510	28.0	5450	61.0	22
12- 8-38	7,700	520	6.8	2470	32.0	4550	59.0	17
12-15-38	7,850	610	7.8	2220	28.3	4810	61.3	22
1- 5-39	11,700	555	4.8	2280	19.5	8700	74.3	41
1-12-39	7,450	745	8.0	2440	29.5	4870	58.8	20
1-19-39	12,550	817	6.5	3740	29.8	7726	61.5	27
1-26-39	9,700	680	7.0	2690	27.8	6000	62.0	22
2-14-39	10,200	690	6.8	2270	22.3	6950	68.0	31
2-21-39	7,400	720	9.8	1205	16.3	5250	71.0	47
2-27-39	6,800	730	10.8	2340	34.3	3480	51.3	10
3- 6-39	7,600	513	6.8	2030	26.8	4925	64.8	24
3-13-39	10,050	603	6.0	2965	29.5	6230	62.0	21
3-20-39	8,600	840	10.8	1680	19.5	5525	64.3	34
2-27-39	7,500	620	8.3	2010	26.8	4700	62.5	23
4- 3-39	9,150	410	4.5	2060	22.5	6425	20.3	31
4-10-39	8,300	685	8.3	1785	21.5	5550	66.8	31
4-25-39	8,150	775	9.5	2340	28.8	4910	60.3	20
5- 8-39	6,500	390	6.0	1450	22.3	4540	69.8	32
5-15-39	10,050	553	5.5	2180	21.8	7180	71.5	32
6- 5-39	6,450	613	9.5	1740	27.0	4050	62.8	23

considered benign, because of apparent but not real interruption in the continuity of the pathologic process. Proof that the continuity is not interrupted is indicated, as already stated, by the presence of bacilli in the gastric contents. Though the lesion resulting from first infection is usually benign, the development of visible evidence of tuberculosis soon after infection, as determined by a positive Mantoux test in one formerly negative, must be seriously considered. To the present time five such individuals have come under observation. All had known recent contact with open cases of tuberculosis, were previously negative to the Mantoux test, developed visible evi-

dence of tuberculosis on roentgenograms, and all had tubercle bacilli in their gastric contents. The only evidence of benignity in these five cases is that none is dead. Two are still receiving pneumothorax and sanatorium treatment; one is on the equivalent of sanatorium treatment at home; one, though showing no recent roentgen-ray change, continues to have positive gastric aspirations; and the other has recently developed, in addition to a clavicular lesion, subminimal infiltrates at the extreme apices. The lesson from these cases supports the opinion that the lesion resulting from the first infection can and in a certain percentage of cases does institute a pathologic process which may continue for years, eventually causing the individual's death.

TABLE VI  
Gastric Contents  
40 Cases

Guinea Pigs	% of Cases	Roentgen-ray		
Positive	45%	Extension	11	61.2%
18		Retrogression	5	27.7%
		No change	2	11.1%
Positive to Negative	30%	Retrogression	7	58.4%
12		Extension	4	33.3%
		No change	1	8.3%
Always Negative	25%	Retrogression	9	90.0%
10		Extension	1	10.0%

#### GASTRIC CONTENTS

As indicated in table 6, 30 of the 40, or 75 per cent, of the subclinical cases were positive by guinea pig inoculation. Where the roentgenogram fails to show changes from month to month, the presence of tubercle bacilli in the gastric contents is the only positive method of indicating that the lesion is both tuberculous and also active. Furthermore, we cannot assume, as we have in the past, that because no change is noted on serial roentgenograms the process is necessarily healed. One student with such a lesion has been under observation for a period of 28 months and, on the seven occasions in which the gastric contents have been aspirated, the results have always been positive.

Where the gastric contents originally have been found positive and have remained positive (table 6), extension occurred in 61 per cent of the cases, and only 28 per cent showed retrogression. Where conversion from positive to negative occurred, retrogression was noted in 58 per cent, and extension in 33 per cent of the cases. In the group always negative on gastric aspiration, retrogression of the lesion was noted in 90 per cent of the cases. The one individual in this group who showed extension (who withdrew from school in 1937) subsequently showed almost complete resolution of the infiltrate.

From the above it appears that examination of the gastric contents by guinea pig inoculation is the most accurate and valuable laboratory method

in determining the status and subsequent course of the subclinical tuberculous lesion.

### SUMMARY

The early tuberculous lesion occurs without producing a clinical picture. Its detection is dependent on repeated roentgen-ray examination of the apparently healthy. The early lesion having been found, the question regarding its status presents itself. Is the process tuberculous, and is it pathologically active or has it healed? Dependence on serial roentgenograms frequently requires the passage of considerable time, and fails to prove that the process is tuberculous. Furthermore, extension means further lung destruction and a less favorable prognosis. Methods, therefore, are desirable which will determine the status of the early lesion before further progression occurs.

Of available laboratory methods, the erythrocyte sediment rate was found to be normal in 90 per cent of the cases, and apparently gives little assurance that a lesion is either benign or inactive. The leukocyte reaction, where favorable, indicates a favorable prognosis. An unfavorable or equivocal leukocyte reaction, however, indicated an unfavorable course in only 50 per cent of the cases. Gastric aspiration with guinea pig inoculation is the most reliable method of proving both the diagnosis and activity of the lesion. The repeated presence of tubercle bacilli in the bronchial secretions usually indicates an unfavorable course. Conversion from positive to negative indicates a more favorable prognosis, and repeated absence of tubercle bacilli in the gastric contents is almost complete assurance of a favorable course.

Close observation and study by laboratory procedures indicate that the lesion resulting from first infection is not always benign and may cause progressive tuberculosis. Maximum information regarding subclinical tuberculosis is dependent on adequate and repeated use of laboratory methods. Relatively little is known of the early lesion or the factors that determine its subsequent course. Many of our present opinions probably will be found fallacious.

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# HEMOLYTIC REACTIONS FOLLOWING TRANSFUSIONS OF BLOOD OF THE HOMOLOGOUS GROUP, WITH THREE\* CASES IN WHICH THE SAME AGGLUTINOGEN WAS RESPONSIBLE †

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THE discovery<sup>16, 17</sup> in 1900 of the isoagglutination reaction was one of the most important steps in the history of blood transfusion, since when donors of the same blood group as the patient are used, transfusions are practically free from danger. Even after this discovery was generally adopted and applied, however, occasional hemolytic reactions continued to occur. In the earlier days, practically all of these reactions could be traced to mistakes in blood grouping (Bordley<sup>4</sup>) of the patient, donor or both, and even at the present time such unnecessary errors are made too frequently.‡ Besides the hemolytic reactions caused by the transfusion of blood of the improper group, others have resulted from the indiscriminate use of "universal" donors.<sup>21, 5, 8, 11</sup> In addition, hemolytic reactions have recently been encountered following transfusions in which patient and donor belonged to the same blood group. Evidently such cases are rare, since only about a dozen definitely established instances of this sort have been reported in the literature to date. (For a review of the literature see reference 37.) The hemolytic transfusion reactions belonging to this last category, namely, those due to "intragroup" incompatibility, are the subject of the present paper.

*Case 1.* The patient was a 52 year old woman, admitted to the surgical service of the Mercy Hospital on August 13, 1939, with the complaint of vomiting, fever and bilateral abdominal pain of eight hours' duration. At the operation, performed on the day of admission, a ruptured solitary ulcer of the ileum§ and peritonitis were found. Resection of the ileum with anastomosis and appendectomy was performed.

The patient belonged to group O. The day after the operation (the second day in the hospital) the patient was given a transfusion of 500 c.c. of fresh citrated blood of group O. Later the same day a second transfusion of 300 c.c. of group O blood was given. A third transfusion of 250 c.c. of blood was given on the third day; a fourth transfusion of 500 c.c. on the eighth day; the fifth and last transfusion of 500 c.c. of blood on the thirteenth day. All of the transfusions were from different group O blood donors. Preliminary to each transfusion the bloods of the patient and prospective donor were cross-matched.

\* Including case cited in addendum.

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‡ With regard to suitable technic of grouping and cross-matching, cf. <sup>38</sup>

§ Separate report in press (Robinson, D. R.: Surg., Gynec. and Obst.).

There were no febrile reactions whatever to the first four transfusions. However, during the week following the operation the patient had a continuous temperature of 103° F., which might possibly have masked the symptoms of a mild reaction. Of significance is the observation that while the hemoglobin concentration rose from 60 per cent on the day of the operation to 82 per cent after the third transfusion, it soon dropped back to 65 per cent and continued to fall after the fourth transfusion. Fifteen minutes after the completion of the fifth and last transfusion there was a severe chill lasting about half an hour, accompanied by a rise in temperature to 104° F. By the next day the patient had hemoglobinuria and marked oliguria, and became noticeably jaundiced (van den Bergh—direct, immediate positive 2.0 units; icteric index 19). The blood urea concentration rose from normal before the transfusion to 163 mg. per cent. The hemoglobin continued to fall, reaching as low as 46 per cent, and despite alkalization the patient died four days after the onset of the transfusion reaction. At the postmortem examination, microscopic sections of the kidneys showed lesions considered characteristic of hemolytic transfusion reactions, namely, the typical degenerative changes of the tubular epithelium and the presence in the lumens of the collecting tubules of casts of brownish, pigmented hematin material.

Before the last transfusion, two cross-matching tests (hanging drop method at 37° C.) were reported by the technician and intern as showing no clumping even for periods up to several hours. Unfortunately, the specimens taken before the transfusion had been discarded inadvertently, and these observations could not be rechecked. Blood obtained from the patient after the transfusion and also after death and a fresh sample of blood drawn from the donor for the last transfusion were tested by one of us (W.). It was possible to confirm the fact that both patient and donor belonged to group O. In the cross-match test, however, while no agglutination was observed in the mixture of donor's serum with patient's cells, by a special technic \* (vide infra) it could be shown that clumping occurred when the patient's serum was added to the donor's cells. Evidently, therefore, the patient's serum contained a special agglutinin, unrelated to the common isoagglutinins,  $\alpha$  and  $\beta$ . That we were not dealing with an autoagglutinin was established by the absence of agglutination in mixtures of the patient's serum with her own cells. With the technics commonly used the abnormal reactions would probably not have been detected.

The properties of the special agglutinin and the corresponding agglutinable property in human blood were then investigated. First of all it was noticed that the reactions were considerably weaker than the common isoagglutination reactions. Moreover, the reactions were most pronounced at low temperatures, no noticeable reaction at all occurring at 37° C. Hemolysis could not be elicited in vitro at any temperature, even after the addition of fresh guinea-pig complement. These properties of the antibody in the patient's serum are somewhat surprising, considering the fact that it was capable of causing a fatal hemolytic reaction (see below). The reactions were best elicited by mixing a drop of a 2 per cent suspension of sensitive cells with two drops of serum in a small test tube (inside diameter 7 mm.) and allowing the mixtures to stand for two hours in the refrigerator. An

\* With the common slide technic the reactions were indefinite.

alternative suitable technic was to chill the mixture for a few minutes, then centrifuge. After gentle shaking, the sediments immediately broke up into a homogeneous suspension in the case of negative bloods, while rather large clumps easily visible to the naked eye persisted with positively reacting bloods. The reactions could easily be reversed by warming the tubes to 37° C.; on chilling, the reactions reappeared.

Blood samples from a number of different individuals have been tested with the patient's serum. Only bloods of group O were selected, on account of the presence in the serum of the isoagglutinins  $\alpha$  and  $\beta$ , which precluded direct tests on bloods of the other groups. It was found that the great majority of bloods were agglutinated by the antibody in question. The agglutinable property involved proved to be unrelated to any of the agglutinogens M, N or P, as well as the agglutinogens A and B. Remarkably, however, the reactions coincided with those given by certain anti-rhesus immune rabbit sera, recently described by Landsteiner and Wiener<sup>20</sup> which define an agglutinable property of human blood designated as Rh.

As will be seen from table 1, in which are given some representative reactions, 14 bloods have been tested with both the patient's serum and the reagent prepared from anti-rhesus immune serum. The chance that the reactions of the two reagents should agree in every instance merely by accident is 1 in 2<sup>14</sup> or about one in sixteen thousand. It is reasonable to conclude, therefore, that the agglutinable property demonstrated with the patient's serum is identical with Rh.

It is now possible to offer an explanation for the hemolytic reaction. The patient belonged to group O (Rh—). Since Rh+ bloods are about 6 or 7 times as common as Rh— bloods, most if not all the donors were probably of group O (Rh+). Apparently, to begin with, the patient had a weak anti-Rh hemolysin in his serum, undetectable by any of the common *in vitro* tests. This assumption would account for the short period of survival of the transfused blood cells, as indicated by the temporary nature of the rise in hemoglobin after the first few transfusions. While one may assume that the blood received in these transfusions was hemolysed too slowly to produce noticeable symptoms, the repeated injections of Rh+ blood served to stimulate the production of anti-Rh antibodies of higher titer, particularly after the fourth transfusion. Accordingly, the fifth transfusion of Rh+ blood gave rise to an acute hemolytic reaction.

Two questions are raised in connection with the above interpretation. The first is why such reactions are not encountered more frequently, as many patients, of whom about one-seventh would be Rh negative, are given repeated transfusions. The probable answer is that not all Rh— individuals are capable of producing Rh antibodies. Some special constitutional factor may be required—possibly the presence of preformed antibodies. In addition, the interval between transfusions must be long enough to permit an adequate rise in titer of the antibody. The second question is how it is possible for an antibody which *in vitro* produces agglutination only at low

TABLE I  
Comparison of Reactions Obtained with Serum of Patient (Case 1) and with an Anti-Rhesus Immune Rabbit Serum

	Type M				Type N				Type MN					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bloods all group O Tests made with	++±	++±	-	++±	++	-	++±	++±	+++	-	++	++±	+++	14
Serum of patient	pos.	pos.	neg.	pos.	pos.	neg.	pos.	pos.	pos.	neg.	pos.	pos.	pos.	-
Anti-rhesus immune serum, diluted 10X and absorbed with half volume of packed sediment of blood No. 14														neg.

The strength of the agglutinations is indicated by the number of plus signs, +++ representing the maximum possible reaction, namely, the formation of a single large clump.



temperatures and of low titer to give rise to a fatal hemolytic reaction. Possibly the agglutinin found in the patient's serum is only an indicator of some supplementary, more subtle mechanism which is brought into play in the body before hemolysis can occur.

Shortly after the above study was completed, a second case, almost an exact counterpart of the first one, was seen at the Mercy Hospital.

*Case 2.* In January 1937, the patient was operated on for a perforated gastric ulcer at another hospital. The postoperative course was complicated by pneumonia and neutropenia, the total white count dropping as low as 3000. A transfusion was given and the white count rose. The patient was discharged after 43 days in the hospital. About six months later, the patient began to have attacks of headache, pain in the lower back and in the legs, these symptoms being accompanied by fever and leukopenia. During the six months before the present admission, the attacks became more frequent and more severe, and the patient had chills occurring at all hours of the day. The temperature ranged from subnormal up to 104° F. and the patient became subject to upper respiratory infections. On November 9, 1939, the patient's tonsils and adenoids were removed; he was discharged on November 11.

On November 22, 1939, the patient was readmitted to the Mercy Hospital on the service of Dr. Pincoffs, because of recurrence of chills and fever three days previously. On November 25, the patient, who belongs to group A, was given a transfusion of 200 c.c. of fresh citrated group A blood. About one hour after this transfusion he had a chill which was slightly more severe than those he had had on the previous few days. However, there was no history of hemoglobinuria. The temperature dropped to a subnormal level 12 hours later and remained subnormal for a week. The patient was given two other transfusions of 250 c.c. each on November 27 and November 30, respectively, both from the same group A donor, but not the donor who gave the blood on November 22. There were no untoward symptoms following these transfusions. The patient had no more chills and felt well until his discharge on December 7.

Two days later the patient was readmitted with the same complaints as formerly, namely chills, fever, headache, etc. On December 12, he was given a transfusion of 200 c.c. of citrated blood from the donor who had given the first transfusion on November 22 (21 days previously). Twenty minutes after this transfusion was completed, the patient presented the symptoms of a severe hemolytic reaction. Hemoglobinemia and hemoglobinuria were present. Almost immediately there was complete suppression of urine, and rather persistent vomiting, at times bloody, ensued. The bleeding and coagulation times were prolonged. The blood urea rose as high as 250 mg. per cent and the creatinine to 14 mg. per cent. After complete anuria for one week there was an output of only 50 c.c. on the eighth day and anuria again on the ninth day. Up to this point the patient had been treated with intravenous glucose, sorbital and diathermy. On the tenth day, following splanchnic block (separate report by Pincoffs and Peters<sup>80</sup>) there was an immediate outpouring of urine and the blood urea dropped to 45 mg. per cent; the creatinine to 1.9 mg. per cent. Thereafter the patient improved progressively.

Previous to each transfusion the bloods of the patient and the prospective donor were cross-matched by the hanging drop and centrifuge methods. After the hemolytic reaction occurred, blood samples taken from the patient and donor before and after the last transfusion were examined by one of us; also the blood of the donor who gave the second and third transfusion was tested. It was found that both donors belonged to group A, subgroup A<sub>1</sub> type M. On the other hand, the patient's blood belonged to group A, sub-

group A<sub>2</sub>, type N. The idea that the difference in the subgroups or in the M-N types was responsible for the reaction could be eliminated at once. Careful analysis of the reactions of the patient's blood revealed that before the fourth transfusion it actually consisted of a mixture of two sorts of blood; namely, about 90 per cent A<sub>2</sub>N blood and about 10 per cent A<sub>1</sub>M blood.\* This indicated that some of the blood from the previous three transfusions was still present in the patient's circulation, which would hardly be possible if either of the agglutinogens A<sub>1</sub> or M had anything to do with the transfusion reaction. Moreover, the proportion of foreign A<sub>1</sub>M cells did not increase after the transfusion given on December 12, which showed that the blood injected on that day must have been completely destroyed.

TABLE II

Cross-Matching Tests of the Serum of the Patient (Case 2) with the Bloods of His Two Donors

Serum Separated From Patient's Blood Drawn	Patient's Own Blood	Tested Against Blood of Donor for 1st and 4th Trans. (Donor No. 1)	Blood of Donor for 2d and 3rd Trans. (Donor No. 2)
Before transfusion	Q.N.S.	±	Q.N.S.
2 days after transfusion	—	—	—
3 days after transfusion	—	—	—
4 days after transfusion	—	++±	—
5 days after transfusion	—	++±	—
6 days after transfusion	—	++±	—
7 days after transfusion	—	++±	—

The tests were made by mixing 2 drops of patient's serum with 1 drop of a 2 per cent blood suspension in a small tube, and allowing the mixtures to stand for two hours at a refrigerator temperature, after which time the reactions were read.

Q.N.S. = quantity not sufficient.

The most logical explanation for these findings was that although both donors were A<sub>1</sub>M, for some reason the blood of the donor used for the first and last transfusions (donor 1) was incompatible, whereas the blood of the other donor (donor 2) was compatible. That this explanation is correct was established by the cross-matching tests. As is shown in table 2, the patient's serum before the fourth transfusion gave at best only a doubtful reaction with the blood of donor 1, and serum obtained shortly after the transfusion gave no reaction at all. However, on the fourth day following the transfusion and thereafter, it could be shown by the sensitive technic described that the patient's serum agglutinated the blood of donor 2 but not the blood of donor 1. No agglutination was observed in mixtures of the patient's cells with the serum of either donor.

A series of individuals was available whose bloods had been tested with the serum of the patient in case 1. Blood samples were drawn from these persons in order to ascertain whether or not the agglutinable property of the blood cells detected by the serum of the patient in case 2 corresponded with the agglutininogen Rh. As is shown in table 3, the reactions of the two sera are identical so that both sera contain the same antibody, anti-Rh.

\* For the technic see: WIENER, A. S.: Blood groups and blood transfusion, pages 55-57.

TABLE III  
Comparison of Agglutination Reactions Obtained with the Sera of the Patients of Case 1 and Case 2

Tests Made With		Bloods (All Group O) of Type													
		M			N		MN								
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Serum From Patient in Case 1		—	++ ++ ++	—	++ ++ ++	++ ++ ++	++ ++ ++	—	++ ++ ++	++ ++ ++	—	++ ++ ++	++ ++ ++	—	—
Serum From Patient in Case 2		—	++ ++ ++	—	++ ++ ++	++ ++ ++	++ ++ ++	—	++ ++ ++	++ ++ ++	—	++ ++ ++	++ ++ ++	—	—

Let us now summarize the second case in the light of the serological findings. A patient, group A (Rh—) was given a series of blood transfusions from two donors, one group A (Rh+) the other group A (Rh—). The first transfusion from the donor A (Rh+) gave rise only to a sub-clinical reaction. The following two transfusions from donor A (Rh—) were perfectly compatible, so that the donor's cells could be demonstrated in the circulation of the patient (with the aid of the M-N tests) for a long time afterwards. On the other hand, the blood from the first transfusion was gradually hemolysed and eliminated, this being accompanied by the appearance of Rh antibodies in the patient's plasma. Later, when a second transfusion of blood from the first donor, A (Rh+), was given, a hemolytic reaction followed. The long interval between the two transfusions from this donor probably allowed time for a fall in the titer of the anti-Rh agglutinins, so that these were not demonstrable either by the hanging drop or centrifuge technic before the last transfusion. The reason why the Rh agglutinins were not demonstrable immediately after the transfusion is that they had been completely absorbed by the Rh+ blood introduced into the recipient's circulation. By the fourth day, however, the antibodies had reformed in sufficient amount to be detectable.

That the property Rh is a true antigen is established by its capacity to stimulate the formation of immune antibodies in our two patients. The anti-Rh agglutinins in the patient's serum had the same properties as most other specific agglutinins, since its activity was not appreciably affected by heating at 56° C. for 30 minutes, and, as shown in table 4, it is absorbable

TABLE IV  
Specific Absorption of the Agglutinin Anti-Rh

Tests Made With	Tested Against			
	Rh Positive Blood		Rh Negative Blood	
	1	2	3	4
Untreated Serum	++±	++±	—	—
Serum Absorbed with Rh+ Blood	—	—	—	—
Serum Absorbed with Rh— Blood	++±	++±	—	—

The absorptions were set up by mixing the patient's serum with one-third volume of packed washed cells in test tubes. After the mixtures had stood for an hour, the tubes were centrifuged in cups containing ice-water, and the supernatant serum pipetted off for the tests. Two drops of serum were mixed with one drop of cell suspensions (2 per cent) in small test-tubes and the readings made after these had stood for two hours in the refrigerator.

by Rh+ blood but not by Rh— blood. The serum from the patient in case 2 like that of the first patient reacted most strongly at low temperatures and not at body temperature. As is shown in table 5, even at ice-box temperature, the reactions were only of relatively low titer. Corresponding

TABLE V  
Titration of the Anti-Rh Agglutinins in the Serum of Patient 2

Tested Against	Dilution of Patient's Serum				
	Undil.	1 : 2	1 : 4	1 : 8	1 : 16
Rh Positive Blood	++±	++	+±	±	—
Rh Negative Blood	—	—	—	—	—

Two drops of each serum dilution were mixed with one drop of cell suspension (2 per cent) and readings were made after the mixtures had stood for 2 to 3 hours in the refrigerator.

with the low titer of the anti-Rh antibody was its lability, for after only one month of storage in the refrigerator, the activity of the serum had diminished noticeably. On the other hand, serum obtained from the patient more than one month after the transfusion was almost as active as the sample originally tested. Three months later, however, the antibody could no longer be detected in the patient's serum.

Of interest is the relative incidence in the general population of Rh positive and Rh negative bloods. In addition to the bloods previously tested with the serum of patient 1, a series of group O and group A bloods was examined with the serum from patient 2. (Group A as well as group O bloods could be tested with the latter serum as it contained no  $\alpha$  agglutinins.) Among a total of 101 individuals (not including the patients or donors of our two transfusion cases) 14 persons were encountered whose bloods did not agglutinate in the anti-Rh sera. This incidence of Rh— bloods (about 1 in 7) closely approximates that previously reported by Landsteiner and Wiener.

Our findings presented above confirm the occurrence of hemolytic reactions after transfusions of blood of the proper group, due to agglutinogens unrelated to the four blood groups. One may also consider that such incompatibilities might be detected before-hand by tests made at low temperatures. In this connection, a case seen by one of us several years ago is of interest.

*Case 3.* The patient was a female child, 4½ years of age, when first referred for blood transfusion by Dr. S. Katz in 1935. The patient first became ill during the winter of 1933 while in Florida, where she is said to have been handled and kissed by a nurse recuperating from acute rheumatic fever. The patient was taken home to Brooklyn where she ran an intermittent and remittent fever. During this illness, the patient also complained of pain and swelling of her thumb. She was treated at the Jewish Hospital for a time, where she was given a blood transfusion without any untoward reaction. Agglutination tests for typhoid, paratyphoid, etc. were negative. The patient recovered 16 weeks after the onset of the illness, following a tonsillectomy.

She again became ill at the end of November 1934, with remittent and intermittent fever ranging as high as 104° F. This was accompanied by migratory joint pains. In January 1935, because of a developing anemia, the patient, who belonged to group A, was given a transfusion of 180 c.c. of blood from a group A donor without

any untoward reaction. (The bloods were also shown to be compatible by the usual open slide technic.) On February 14, 1935, the patient was given a second transfusion of 100 c.c. of blood from the same donor (after re-grouping and cross-matching the bloods). One hour after this transfusion, the patient had a severe chill and the temperature rose to 106° F. As reexamination of the bloods of patient and donor again corroborated the previous results, this was interpreted as a non-specific reaction, the clinical condition being blamed as a contributing factor. After the transfusion the patient's temperature remained normal for two days, then intermittent fever ranging up to 105° F. and 106° F. recurred and continued for two weeks. As the patient's hemoglobin was dropping and her clinical condition continued downhill, a third transfusion of 150 c.c. of blood was given from the same donor. This was followed by a sharp chill, rise in temperature to 107° F. and hemoglobinuria. The patient developed a hemorrhagic tendency, and blood oozed from all puncture wounds, including that of the transfusion, and from the mucous membranes. Another transfusion seemed urgently needed, but since retests again proved patient and donor to belong to group A, and the cross-matching tests were again negative, this idea was abandoned, there being no assurance that a different donor's blood would not also be incompatible. (Indeed additional tests even showed that the bloods of recipient and donor both belonged to subgroup A<sub>1</sub> and type MN, so that neither the subgroups nor the properties M and N could be implicated as the cause of the reaction.) The oozing of blood continued and the patient died two days later from exsanguination.

In the case just described, it seems certain that the hemolytic reaction must have been due to the appearance in the patient's plasma of immune iso-antibodies for the donor's blood cells. It is possible that agglutinins might have been demonstrable in the recipient's serum, if the sensitive technic outlined in the present paper had been used; namely, incubation of the mixtures of serum and cells in the refrigerator, with or without centrifugation. Possibly the cases reported by DeGowin and Baldrige,<sup>9</sup> Johnson and Conway,<sup>13</sup> and Goldring and Graef,<sup>10</sup> etc., could have been explained in a similar way. However, there is evidence that not all intra-group transfusion reactions can be traced to the formation of Rh antibodies in a Rh-individual. For example, in Zacho's case,<sup>41, 42</sup> the agglutination reactions given by the patient's serum were of highest titer at 37° C. and weakest at low temperatures. Aside from this peculiarity of the antibody, the difference in the frequency of bloods containing the agglutinable factor proves that the property Rh played no part in the reaction. The appearance following a transfusion of an immune isoagglutinin with properties similar to those of Zacho's case has been reported by Neter.<sup>27</sup> With regard to the transfusion reaction reported by Mandelbaum,<sup>23</sup> the blood of the patient was retested by us and found to be Rh positive. Accordingly the property Rh cannot be blamed for that reaction either. In the case reported by Levine and Stetson,<sup>22</sup> the incidence of bloods agglutinable by the patient's serum (based on 104 tests) was about 80 per cent, which is not significantly different from the frequency of Rh plus blood (about 85 per cent), but the antibodies gave just as intense reactions at 37° C. as at low temperatures. Whether or not the agglutigen Rh was the responsible factor in the two cases reported by Culbertson and Ratcliffe<sup>8</sup> or in the cases reported by Bauer<sup>2</sup> cannot be decided from the data given in their papers. As to Mosonyi's report<sup>28</sup> of a hemolytic reaction fol-

lowing repeated transfusions of group B blood to a group B patient, the writer's conclusion that the reaction was due to the formation of immune isoagglutinins specific for group B blood is not intelligible to the present authors.

In addition to those cases where hemolytic reactions followed repeated transfusions of blood of the homologous group, there are a number of reports of intra-group hemolytic reactions in patients who had never received a previous blood transfusion, or where the previous transfusion had been given so long ago (several years) that they could hardly be blamed for the reaction. Such instances have been reported by Zacho,<sup>41</sup> Parr and Krischner,<sup>20</sup> Culbertson and Ratcliffe,<sup>6</sup> McCandless,<sup>25</sup> Johnson and Conway,<sup>13</sup> Smith and Haman,<sup>34</sup> Mandelbaum<sup>23</sup> and Levine and Stetson.<sup>22</sup> Remarkably enough in all of these cases except the one reported by McCandless\* the patients were women who had recently given birth or had had a miscarriage.† Culbertson and Ratcliffe remarked concerning this coincidence in their two cases but did not attempt any explanation. In the case reported by Levine and Stetson, the patient, who had just had a stillbirth, was transfused with blood from her husband and a hemolytic reaction resulted. These authors suggest that the fetus inherited an antigenic substance from the father which was lacking in the mother, and the latter became immunized to the antigen after carrying the fetus for a long time after it had died in utero. In support of their interpretation that the agglutinin found in their patient's serum was an immune antibody rather than a natural one, Levine and Stetson cite the gradual drop in its titer and its eventual complete disappearance several months after the transfusion. In the other instances referred to above, a similar explanation may hold, though the individual antigenic differences responsible need not be the same in every case.

In support of this idea can be cited the report by Jonsson,<sup>14</sup> who found the average titer of the isohemolysins  $\alpha$  and  $\beta$  to be higher than normal in women who had recently given birth, and who attributes this phenomenon to the specific stimulation provided in instances of heterospecific pregnancy. If the presence of a group A or group B fetus in a group O mother can cause a rise in titer of the isoantibodies  $\alpha$  and  $\beta$ , respectively, it does not seem improbable, that, for example, a Rh— woman carrying a Rh+ fetus might

\* With regard to the McCandless case, this is actually not an instance of an intragroup hemolytic reaction, since retests of the donor's blood by Hoxworth<sup>12</sup> have shown that the donor actually belongs to group A (subgroup  $A_2$ ) not to group O as stated in the original case report. The case reported by Von Deesten and Cosgrove<sup>36</sup> of renal insufficiency following a blood transfusion is not a true hemolytic reaction since the hemoglobin rose from 70 per cent before the transfusion to 87 per cent after the transfusion. The rise in hemoglobin resulting from the transfusion corresponds closely with the predicted rise from a transfusion of 750 c.c. of blood, which was the amount given. If hemolysis had occurred there should have been no rise in hemoglobin. Moreover, the symptoms were not typical of a transfusion reaction and could be more logically attributed to the slight kink of the right ureter detected subsequently by pyelogram.

Incidentally, Thalheimer's case<sup>35</sup> frequently cited as an example of the danger of repeated blood transfusions from the same donor is not an example of an intragroup reaction, since the donor belongs to group B and the patient to group O.

† While this paper was in press, our attention was called to another instance of intra-group incompatibility reported by Pondman,<sup>43</sup> occurring in a postpartum case.

react by producing Rh antibodies. However, the paucity of reports of intra-group hemolytic reactions even in postpartum cases indicates that this phenomenon must be rare. Possibly in normal pregnancy the placenta offers a barrier to the passage of antigens from fetus to mother, and, in addition, as pointed out above, because of constitutional differences not all individuals will respond to the foreign antigens by producing specific antibodies.

An important question is what bearing other known individual differences of human blood, namely, those dependent on differences in the agglutinin A ( $A_1$  and  $A_2$ ) and on the agglutinogens M, N and P, have on the occurrence of intra-group transfusion reactions. With respect to the subgroups of groups A and AB, it has been shown by Landsteiner and Levine<sup>18</sup> that a small percentage of individuals belonging to these groups have in their plasma irregular agglutinins acting on blood of the opposite subgroup. Some writers<sup>3,7</sup> assert that differences in the subgroups can cause hemolytic reactions and warn that only donors of the homologous subgroup be used for transfusions. As a matter of fact no case has yet been reported where the subgroups were conclusively proved to be responsible for a serious reaction. In our own experience with over 3,000 transfusions<sup>30</sup> the incidence of even minor reactions among patients of group A when donors are selected without regard to the subgroups is not significantly higher than among patients in groups O and B, the blood cells of the donor persisting in the patient's circulation whether donor and recipient belong to the same or different subgroups. Similar has been the experience of Hoxworth<sup>12</sup> in a series of 2950 transfusions. As is illustrated by case 2, in hemolytic transfusion reactions, even if it is found that patient and donor are not in the same subgroup this does not prove the difference in subgroups to be responsible. To the best knowledge of the writers, no report has appeared in the literature which proves that agglutinin A, can be antigenic for  $A_2$  persons, or vice versa, but recently two such cases have come to our personal attention.<sup>30</sup> One patient (of subgroup  $A_2$ ) had received repeated transfusions of  $A_1$  blood; the other (also of subgroup  $A_2$ ) was a postpartum case. Both had  $\alpha$  agglutinins in their sera of titer 16 at room temperature. Accordingly, the most practical procedure, and the one followed by us, is to disregard the subgroups when selecting donors for transfusion except in the infrequent cases where the patient's plasma contains the irregular isoagglutinins  $\alpha_1$  or  $\alpha_2$  and then to use donors of the homologous subgroup. Such instances can be detected by the usual cross-matching tests.

With regard to the agglutinogens M and N, the situation is similar. Despite the performance of hundreds of thousands of transfusions every year, in which donors are selected without regard to their M-N types, not a single hemolytic reaction can be traced to this source. The report by Martinet<sup>24</sup> that he observed the formation of specific hemolysins for M and N following transfusions is unconvincing, and in the present authors' experience repeated injections of type M blood into type N individuals or vice-versa has not stimulated the production of isoantibodies for M or N. Evi-



dently, therefore, these agglutinogens, unlike A and B, are not antigenic, or at most very feebly antigenic, for human beings. Accordingly, the prominence given them by certain writers<sup>31</sup> as a possible source of hemolytic reactions after repeated transfusion is not warranted, though the possibility that such cases may ultimately be found cannot be excluded. Only three cases (among hundreds of thousands of persons tested) are known of human beings with natural anti-M isoagglutinins, none having been encountered to date with anti-N agglutinins. In patients with such isoagglutinins, it would of course be wise to take the agglutinogens M and N into account when selecting the blood donor.

At least one case is known where the injection of blood containing agglutinin P into an individual lacking the agglutinin stimulated the formation of isoantibodies for P. In this case, seen by Dr. S. H. Polayes, there was difficulty in finding a compatible donor for a patient of group A, since her serum agglutinated most other bloods of group A. This patient had had a previous transfusion without untoward reaction from a group A donor whose cells were now also agglutinated by her serum. The patient's blood was referred to one of us<sup>30</sup> for study and it was found that the abnormal reactions of its serum corresponded with the agglutinin P. For this patient, accordingly, only blood of group A(P—) would be suitable for transfusion.

With regard to the rôle played by irregular agglutinins in general in hemolytic reactions, it may be said that they show marked differences as to their significance in transfusions. In a number of instances<sup>18, 19</sup> where patients were transfused with blood acted on by atypical agglutinins in their sera, no untoward symptoms resulted, although the *in vitro* reactions were at times as strong as those described here. This indicates the existence of some as yet undescribed qualitative difference among the various irregular isoantibodies.

No evidence exists that pseudoagglutination (or pronounced rouleaux-formation) can cause untoward transfusion reactions. Also, in the authors' experience autoagglutinins have not caused hemolytic reactions. (In patients with autoagglutinins, however, we take care to keep the blood at body temperature during its infusion, while ordinarily we are content with blood at room temperature.) Indeed, injudicious attempts to warm up the blood as a routine are dangerous, and in at least one case the injection of blood damaged by overheating gave rise to a fatal hemolytic reaction.<sup>1</sup> Another non-specific cause of severe or even fatal hemolytic transfusion reactions that has come to the fore in recent years is the use of preserved blood stored for too long periods of time before injection. As is pointed out elsewhere,<sup>33, 40</sup> the safe time limit for the storage of blood for transfusion is between five and 10 days.

## DISCUSSION

The danger of intra-group hemolytic reactions has been shown to be greatest in patients receiving repeated blood transfusions and in postpartum

cases. With regard to the warning<sup>15</sup> not to use the same donor for patients receiving repeated transfusions, our findings show that this measure is not sufficient to exclude transfusion reactions, since the antigens responsible may occur in a considerable percentage of individuals. In fact, the patients in cases 1 and 2 would have been safer with repeated transfusions from a single Rh— donor. With regard to the postpartum patients who had hemolytic reactions following transfusions of blood of the proper group, though never transfused previously, these should belong to the same category as the patients immunized by repeated transfusions, if the theory suggested is correct; namely, that the patients became immunized while the fetus was in utero to antigens shared by fetus and blood donor (usually the husband) but absent from the patient's body. Incidentally, some writers consider leukemia and hemolytic icterus contraindications to blood transfusion, as hemolytic reactions have been observed following transfusions of apparently compatible blood in these diseases. The formation of immune isoantibodies seems the most plausible explanation for these observations, because such patients are usually given many blood transfusions.

With regard to the prophylaxis of intra-group hemolytic reactions, no single in vitro technic will cover every exigency, as while most of the irregular isoagglutinins act best at low temperatures, others have been found that react more strongly at body temperatures. However, the following technic of cross-matching is advised in addition to the usual grouping and cross-matching tests, as it will anticipate most reactions of this sort.

1. Two drops of patient's serum, preferably separated from the clot at refrigerator temperature, are mixed with one drop of donor's cell suspension in a small test tube.

2. In a second tube a similar mixture of patient's serum and patient's cells is set up.

The tubes are placed in ice-water for 5 minutes, then centrifuged while still cold and the mixtures are gently shaken. The reactions are read both macroscopically and microscopically. If neither tube shows a reaction, the donor is compatible. If both show a reaction, we are dealing with an autoagglutinin and the donor probably can be used without danger. If tube 1 shows agglutination and tube 2 does not, the donor is incompatible and others must be tested in order to find a suitable one.

In any event, in patients receiving repeated transfusions and in postpartum cases the serological test should be supplemented by a biological test,<sup>28</sup> if time permits. In citrate transfusions it is a simple matter to inject the first 50 or 100 c.c. of blood very slowly in order to determine whether a reaction will occur. If a chill\* results, the infusion should be stopped and another donor tried. This procedure would probably prevent any serious consequences since 100 c.c. of incompatible blood are hardly enough to cause a fatal reaction. In a series of 15 hemolytic reactions with 10 fatalities analysed by Bordley, all patients receiving less than 350 c.c. of blood recovered.

Our findings are also of interest since they demonstrate by another method the large number of individual differences in human blood. With

\* A chill caused by a blood transfusion usually begins within an hour.

the agglutinogens A<sub>1</sub>, A<sub>2</sub>, B, M, N, P and Rh alone as many as 72 different types of human blood are readily distinguished. Also remarkable is the correspondence between the reactions of the sera of our two patients and the anti-rhesus immune sera prepared by Landsteiner and Wiener.

### SUMMARY

Three cases are reported in which repeated transfusions of blood of the proper group gave rise to hemolytic reactions, two of the three reactions resulting in the death of the patient.

In two cases there was noted the appearance in the patient's serum of an isoagglutinin designated as anti-Rh. This is explained as the immune response to the injection of Rh+ blood into Rh— individuals, the blood group playing no rôle. Following the appearance of the anti-Rh agglutinins the transfusion of Rh+ blood gave rise to hemolytic reactions. Remarkably the reactions of the anti-Rh sera corresponded with those of immune rabbit sera prepared by Landsteiner and Wiener by the injection of rhesus blood. The frequency distribution of agglutininogen Rh in the general population is approximately 85 per cent Rh+ and 15 per cent Rh—.

Our cases were compared with others reported in the literature and various similarities and differences pointed out. A hypothesis is offered to explain the occurrence also of hemolytic intra-group reactions in certain individuals who had not received previous blood transfusions. The rôle played by the properties A<sub>1</sub>, A<sub>2</sub>, M, N and P in transfusion reactions is discussed. Methods are suggested for the prevention of occurrence of intra-group hemolytic reactions.

### ADDENDUM

While this article was in press, an additional case of intragroup incompatibility, based on individual blood differences with respect to the property Rh, was observed. The history of this case is as follows:

*Case Report.* The patient was a woman, 58 years of age, admitted to the private service of Dr. Frank Teller at the Jewish Hospital of Brooklyn, with the diagnosis of diabetic gangrene of the toes of one foot. Amputation was performed, and following the operation, the patient's condition was poor. A transfusion of 500 c.c. of citrated, group A, compatible blood was given by the gravity method. Despite the transfusion, the hemoglobin dropped from 78 to 70 per cent; the red blood cell count from 3.95 million to 3.14 million per cu. mm. Following this transfusion, which was given on April 18, 1940, there was no detectable untoward reaction. On April 25, a second transfusion was performed; this time 300 c.c. of group O blood were given. One hour after the transfusion, the patient had a severe chill lasting 30 minutes, and there was an abrupt rise in temperature. Moreover, again there was no appreciable improvement in the hemoglobin or red count, and it was decided to investigate the cause of this transfusion reaction in greater detail.

The grouping tests revealed:

Blood of	Group	Subgroup	Type
Patient.....	A	A <sub>2</sub>	M
1st donor (patient's son).....	A	A <sub>2</sub>	MN
2d donor (professional).....	O	—	M

It is clear that the fate of the blood received at the first transfusion could be determined by testing the patient's blood with anti-N serum; the fate of the blood received at the second transfusion by tests with anti-A serum. Tests made on a sample of blood drawn four days after the second transfusion showed that all the blood received at the two transfusions had been eliminated from the circulation, while transfused cells ordinarily survive for periods up to three and four months. This indicated the existence of some incompatibility between the blood of the patient and those of the two donors. Tests were then set up by the centrifuge method in the cold, and it was found that while no agglutination occurred in mixtures of the patient's serum with her own cells, strong clumping was evident in the tubes containing the bloods of the donors. This phenomenon was evidently connected in some way with the transfusion reaction, and supplied the key to the explanation for the rapid disappearance of the donors' cells from the patient's circulation. A series of blood specimens from individuals who had previously been tested for the property Rh was then tested with the patient's serum, and the results proved that we were dealing once more with an incompatibility reaction based on the property Rh.

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# THE CARDIAC OUTPUT IN CONGESTIVE HEART FAILURE AND IN ORGANIC HEART DISEASE \*

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THE mechanism of heart failure is still the subject of investigation. In recent years, however, observations have been made which lead to a clearer understanding of its pathological physiology. In 1932 Stewart and Cohn<sup>1</sup> published data showing that in human beings "The volume output of blood per minute from the heart which is in failure is diminished and its size larger than when it is in a state of compensation." In addition, there were certain observations relating to dogs pointing to the same conclusions.<sup>2</sup> Since then Stewart and his associates<sup>3</sup> have made further investigations of patients suffering from congestive heart failure which contributed to the same notion. We have continued our studies of this subject and now bring together our data relating to it.

In our observations we have related certain objective measurements of the circulation to the several functional states which can be recognized clinically in patients suffering from cardiac disease. For instance, certain patients exhibited signs of organic heart disease but had never experienced congestive failure; in others, observations were made in the presence of congestive heart failure; in others, after recovery from failure; and in another group studies were made both during and after recovery from failure. Representative patients of each of the four most common etiological rubrics, namely rheumatic fever, arteriosclerosis, hypertension and syphilis, were observed, those exhibiting normal sinus mechanism as well as those in whom auricular fibrillation prevailed.

## METHODS

All observations were made in the morning while the patients were in a basal metabolic state. Measurements of the cardiac output were made by the acetylene method, three samples of gas being taken, as recommended by Grollman<sup>4</sup> in his book entitled "The Cardiac Output of Man in Health and Disease," and as further elaborated by Grollman, Friedman, Clark and Harrison.<sup>5</sup> During this measurement the patient sat in a steamer chair (at an angle of 135 degrees) with the legs extended. Each patient was made familiar with and trained to carry out the procedures beforehand. While

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he was resting quietly, the radial pulse was counted at intervals of five minutes. At the end of one-half hour the acetylene-air-oxygen mixture was rebreathed. The amount of gas in the "rebreathing bag" was adjusted to the amount the patient could breathe satisfactorily. Three samples of gas were obtained during each period of rebreathing for estimation of the arteriovenous oxygen difference. Three periods of rebreathing were carried out to make certain that mixing was secured; one, two or all sets were analyzed. The arteriovenous oxygen differences in those in which checks were secured were averaged. Satisfactory checks can be secured by this method in the grade of heart failure which we studied (figure 1). Shortly

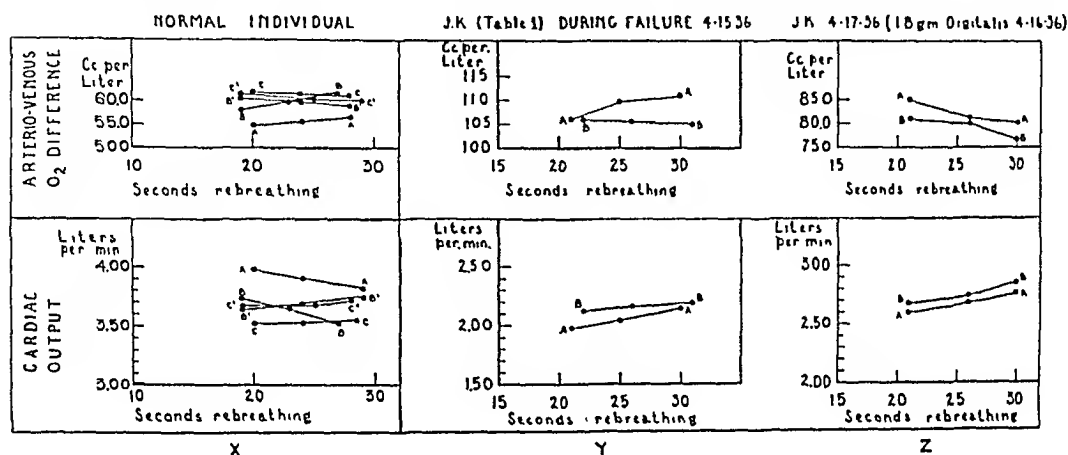


FIG. 1. In this figure are shown data relating to the application of the Grollman 3 sample technic to patients suffering from heart failure. In figure 1X are data obtained from a normal individual for comparison. Rebreathings A, B and C were secured in succession on 4-8-35, B<sup>1</sup> on 4-9-35 and C<sup>1</sup> on 4-10-35. The first point on each curve represents the arteriovenous oxygen difference calculated from the first and second samples of a rebreathing, and the third, that is to say the last point, from the second and third samples. The point in the middle is the average of the two. The cardiac outputs correspond to these arteriovenous oxygen differences. It is apparent that the arteriovenous oxygen differences and cardiac outputs agree, not only on the same day but also on successive days. In figure 1Y are plotted in a similar fashion data of J. K. (table 1) during heart failure. Satisfactory checks were secured. In figure 1Z are plotted data of J. K. (not given in table 1) secured on 4-17-36 after the patient had been given 1.8 gm. digitalis and clinical improvement had occurred. Checks were again obtained. The arteriovenous oxygen differences have decreased and the cardiac outputs increased as compared with data of 4-15-36.

after the rebreathings, the oxygen consumption was measured with a Benedict-Roth spirometer. After a short pause the vital capacity was measured, and the height and the weight were recorded. Then the patient rested again, this time by lying down. In succession, sufficient time being allowed between each procedure for the patient to return to a basal metabolic state, an electrocardiogram was taken, the arm to tongue circulation time recorded, the venous pressure estimated and the blood pressure measured; finally, the basal state still being maintained, a roentgenogram of the heart was made at a distance of 2 meters.

The arm to tongue circulation time was estimated by the use of decholin sodium<sup>6</sup>; 5 c.c. of a 20 per cent solution were injected rapidly (one to two

seconds) through an 18 gage needle into an antecubital vein while the patient was lying quietly in a supine position. This was repeated one and one-half minutes after the response to the first test had been elicited. The time was recorded from the beginning of the injection until the patient perceived the bitter taste. The injection time was also recorded; since, however, the response may come with a minimal amount of the drug, the time which we used was measured from the start rather than from the conclusion of the injection.

The venous pressure was measured by the direct method,<sup>7</sup> a large antecubital vein being used and the arm being placed on a level with the right auricle. The apparatus consisted of an L tube of glass attached to a three way stopcock, a syringe and an 18 gage needle. The apparatus was filled with a sterile normal solution of sodium chloride, venipuncture was performed, and the direct pressure readings were recorded. Normal pressures with this apparatus range from 4 to 10 cm. of saline solution. The antecubital vein of one arm was reserved for the injection of decholin and that of the other arm for the measurement of venous pressure. In subsequent measurements the vein was entered at the site first punctured.

Roentgenograms of the cardiac silhouette were taken with the patient in the standing position, during full inspiration, at a distance of 2 meters.\* Measurements of the cardiac area were carried out by the technic of Levy,<sup>8</sup> and estimations of volume were made as recommended by Bardeen.<sup>9</sup>

The work of the left ventricle per beat was calculated by making use of the formula<sup>10</sup>:  $W = QR + (wV^2/2g)$ , in which  $W$  equals the work done per beat;  $Q$  equals the volume of blood expelled per beat;  $R$  equals the mean arterial blood pressure in millimeters of mercury times 13.6;  $V$  equals the velocity of blood in the aorta;  $w$  equals the weight of the blood, and  $g$  equals the acceleration due to gravity. The last part of the formula,  $wV^2/2g$ , was omitted.<sup>11</sup>

#### PLAN OF OBSERVATIONS

Observations were made of certain patients who suffered from organic heart disease, but who had never experienced heart failure, and of patients who had recovered from heart failure at some time in the past. Certain of these patients were admitted to the hospital in the afternoon and underwent training for the procedures which were to take place in a basal state the following morning. Others of them, if they lived in the neighborhood, came to the hospital on one occasion for training, and rode in a taxicab to the hospital without breakfast on the morning the observations were to be made; they rested one hour after their arrival. Those patients who were studied both during failure and after recovery from failure, as well as those in the hospital concerning whom data were collected only during failure or only after recovery from failure, were all treated in a uniform fashion<sup>12</sup> with

\* The authors are deeply indebted to the Roentgen-Ray Department of the New York Hospital for their cooperation in this investigation.



TABLE I  
Data Relating to Patients Suffering from Congestive Heart Failure

Name	Age	Sex	Date	Oxygen Consumption	Arterio-venous Oxygen Difference	Cardiac Output	Cardiac Output	Heart Rate	Stroke Volume	Arterial Pressure
				c.c. per min.	c.c.	l./min.	l./sq.m./min.	per min.	c.c.	mm. Hg
<i>Hypertensive Group</i>										
A. F.	38	M	1/ 4/36	286	110.9	2.58	1.59	94	29	211/145
M. R.	68	M	1/21/36	274	117.6	2.33	1.27	120	20	170/94
M. H.	53	M	11/23/35	280	98.3	2.85	1.66	82	35	153/110
F. G.	51	M	3/ 5/36	263	81.4	3.23	1.62	68	47	160/110
L. B.	64	M	2/29/36	249	82.8	3.01	1.70	100	30	200/114
<i>Arteriosclerotic Group</i>										
C. K.	48	M	11/13/35	212	88.9	2.38	1.50	114	21	97/78
F. St. J.	73	M	9/25/35	245	94.4	2.60	1.37	60	43	150/90
<i>Luetic Group</i>										
J. K.	55	M	4/15/36	220	107.5	2.05	1.26	98	21	156/40
F. K.	61	M	2/28/35	240	83.1	2.89	1.45	119	24	174-160/110
<i>Rheumatic Group</i>										
S. S.	32	M	2/19/36	245	115.3	2.13	1.23	70	30	114/76
W. B.	32	F	4/28/36	207	106.3	1.95	1.32	80	24	110/80
W. H.	24	M	9/23/35	263	92.8	2.83	1.93	110	28	94/70
C. S.	29	F	4/24/36	185	113.8	1.63	1.07	98	17	102/82
J. G.	28	M	3/13/35	272	95.2	2.86	1.82	102	28	150-130/90
L. C.	30	F	3/ 4/35	222	96.8	2.29	1.38	100	23	120-110/74
M. C.	53	F	1/28/36	207	102.9	2.01	1.25	100	20	170/100
G. MacF.	57	M	2/25/36	189	84.2	2.24	1.47	64	27	110/90
J. M.	37	M	2/27/34	203	100.5	2.02	1.17	76	27	140/80
M. P.	41	F	4/30/34	180	90.6	1.98	1.28	124	16	112/70
B. D. §	49	F	3/12/36	180	82.0	2.20	1.51	46	48	122/70
S. C. §	39	F	3/23/36	166	67.8	2.45	1.74	64	38	108/66
A. G.	34	M	4/20/35	317	147.8	2.14	1.17	160	13	94/64
M. P.	40	F	11/20/37	205	101.9	2.01	1.16	94	22	110/80
A. C.	32	M	1/ 5/38	171	91.9	1.86	1.21	78	24	90/65
			3/27/35	278	119.8	2.32	1.28	150	15	94/56

\* The cardiac volume has been multiplied by the constant in Bardeen's formula.

† In this column the following abbreviations are used:

Rh. = rheumatic fever

Unk. = unknown

Hypt. = hypertension

Artscl. = arteriosclerosis

R-I-V-HB = right intra-ventricular heart block

M.S. = mitral stenosis

M.I. = mitral insufficiency

A.S. = aortic stenosis

A.I. = aortic insufficiency

Enl.Ht. = enlargement of the heart

‡ 0, +, ±, ↓, ↑, = absent, present, doubtful, decreased, increased, respectively.

§ This patient, unlike the others in this group, was under the influence of digitalis when the special studies of the circulation were made.

TABLE I (Continued)

Data Relating to Patients Suffering from Congestive Heart Failure

Left Ven-tricular Work	Circulation Time	Venous Pressure	Vital Capacity	Cardiac Area	Cardiac Volume *	Diagnosis †	Signs ‡						Rhythm
							Dyspnea	Cyanosis	Rales	Liver	Edema	Fluid in chest	
gm.m./per beat	sec.	cm.	c.c.	sq.cm.	c.c.								
<i>Hypertensive Group</i>													
76.0	22.3	21.0	1400	167.2	1044	Hypt.; Enl. Ht.	+	0	+	+	0	0	N.R.
36.0	25.9	21.3	1600	172.3	1091	Artscl.; Enl.Ht.; Hypt.	+	±	+	+	0	0	N.R.
63.0	35.1	10.7	1900	218.2	1555	Artscl.; Hypt.; Enl.Ht.; R-I-V-HB	+	+	+	+	+	+	N.R.
86.0	50.0	21.5	2700	234.2	1730	Hypt.; Enl.Ht.	+	+	+	+	+	0	N.R.
66.0	15.8	18.6	1300	141.1	809	Artscl.; Hypt.; Enl.Ht.	+	+	+	+	±	0	N.R.
<i>Arteriosclerotic Group</i>													
25.0	30.0	19.0	2300	176.2	1130	Artscl.; Enl.Ht.	+	+	0	+	+	0	N.R.
70.2	55.0	14.8	1200	166.6	1039	Artscl.; Enl.Ht.	+	+	+	+	+	0	A.F.
<i>Lutic Group</i>													
28.0	25.8	18.3	1500	204.5	1420	Syphilis; A.I.; Enl.Ht.	+	+	+	+	+	+	N.R.
44.6	20.1	17.3	2200	198.0	1346	Aneurysm; Enl.Ht.	+	+	+	0	+	0	N.R.
<i>Rheumatic Group</i>													
39.0	42.6	18.1	3200	215.6	1528	Rh.; M.S. and M.I.; Enl.Ht.	0	+	+	+	0	0	N.R.
31.0	27.0	17.0	1500	194.2	1317	Rh.; M.S. and M.I.; Enl.Ht.	+	+	+	+	+	±	N.R.
29.0	26.6	5.8	2700	220.5	1579	Rh.; M.S. and M.I.; Enl.Ht.	+	+	0	+	0	0	N.R.
21.3	36.4	24.8	1700	206.3	1430	Rh.; M.S. and M.I.; Enl.Ht.	+	+	+	+	+	0	N.R.
43.8	25.4	23.2	2600	164.3	1019	Unk.; M.S. and M.I.; Enl.Ht.	+	+	+	+	+	+	A.F.
31.3	22.5	6.6	2750	202.9	1399	Rh.; M.S. and M.I.; Enl.Ht.	+	+	0	+	+	0	A.F.
36.7	34.0	11.4	1550	194.2	1320	Rh.; M.S. and M.I.; Hypt.; Enl.Ht.	0	+	+	+	+	+	A.F.
36.7	24.0	7.9	1750	158.6	965	Rh.; M.S. and M.I.; Enl.Ht.	0	+	+	+	0	0	A.F.
40.4			2700	218.0	1554	Rh.; M.S. and M.I.; Enl.Ht.	+	+	+	+	0	0	A.F.
19.8			2080	173.2	1102	Rh.; M.S. and M.I.; Enl.Ht.	0	0	+	+	0	0	A.F.
62.6	25.4	10.3	2000	148.6	876	Unk.; M.S. and M.I.; Enl.Ht.	+	+	0	+	0	0	A.F.
45.0	20.2	15.8	2000	153.6	918	Unk.; M.S. and M.I.; Enl.Ht.	+	+	0	+	+	0	A.F.
14.4	33.4	22.7	2700	258.6	2008	M.S. and M.I.; Enl.Ht.	0	+	0	+	0	0	A.F.
28.4	27.5	25.0	1400	180.9	1172	Rh.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.	0	+	+	+	+	+	N.R.
25.5	24.7	13.9	1900	173.3	1120		0	0	+	+	0	0	N.R.
15.3	28.0	7.2	3500	171.9	1090	M.S.; M.I.; A.I.; Enl.Ht.	+	+	+	+	0	0	A.F.

respect to use of fixed fluid and limited salt intake, and to the use of digitalis in a uniform manner.\*<sup>3, 12</sup> In estimation of the average values, those in whom the diagnosis was rheumatic heart disease make up a group, and those in the hypertensive lutic and arteriosclerotic rubrics have been considered together as a miscellaneous group, and finally the average of all groups combined has been taken.

Data are recorded in tables 1, 2, 3 and 4.

\* They had been given 1.6 to 1.8 gm. of digitalis (New York Heart Association) within 24 hours as the digitalizing amount and on the average 0.2 gm. a day as the maintenance amount.<sup>3, 12</sup> The method of treatment is not expanded because observations were made during failure and after recovery from failure in order to compare the two states.

TABLE II

Mean Values of Measurements of Normal Individuals \* and Patients Suffering from Heart Disease (tables 1, 3, and 4)

Classification†	Arterio-Venous Oxygen Difference (c.c.)	Cardiac Index (liters per minute)	Stroke Volume (c.c.)	Venous Pressure (cm. normal saline)	Circulation Time (sec.)
Normal Individuals (16 observations on 11 subjects)	61.5	2.09	59	10.1	14.4
Heart Disease before Failure (46 observations on 39 patients)					
Rh.	73.0	1.83	42	8.7	15.0
Hypert., Arterioscl., Syph.	64.4	2.05	50	6.2	16.6
Rh., Hypert., Arterioscl., Syph.	71.4	1.87	43	8.1	15.4
Heart Disease Recovered Failure (31 observations on 23 patients)					
Rh.	79.9	1.65	43	7.1	21.5
Hypert., Arterioscl., Syph.	72.6	1.88	44	7.5	26.2
Rh., Hypert., Arterioscl., Syph.	76.9	1.73	44	7.3	23.7
Heart Disease during Failure (25 observations on 24 patients)					
Rh.	100.0	1.37	25	15.0	28.4
Hypert., Arterioscl., Syph.	96.1	1.49	30	18.1	31.3
Rh., Hypert., Arterioscl., Syph.	99.0	1.42	27	16.2	29.6

\* Data from Stewart, H. J. and Watson, R. F.<sup>13</sup>

† Rh. Hypert., Arterioscl., Syph. = Rheumatic fever, Hypertension, Arteriosclerosis, Syphilis, respectively.

### OBSERVATIONS MADE DURING HEART FAILURE

There are 25 observations on 24 patients belonging to four etiological groups, namely rheumatic, hypertensive, luetic, and arteriosclerotic (tables 1 and 2; figures 2 *a*, *b*, *c*). The average cardiac index ‡ for all etiological groups was reduced to 1.42 liters (2.09 liters in normal individuals), being 1.37 liters for the rheumatic group, and 1.49 liters for the miscellaneous group.

The average arteriovenous oxygen difference was increased to 99.0 c.c. for all groups, and was 100.0 c.c. and 96.1 c.c. when separated into rheumatic and miscellaneous rubrics (average normal, 61.5 c.c.).

‡ Cardiac index = cardiac output in liters per square meter of body surface.

FIG. 2. In this figure are plotted as frequency diagrams the data relating to measurements of the circulation in the group of normal individuals and in the heart disease groups (tables 1, 2, 3, and 4). In this figure, as well as in figure 3, each square is a unit and represents one measurement, and they are piled on top of one another when there is recurrence of that increment in that group. The increments are as follows: arteriovenous oxygen difference, 5 c.c.; cardiac index, 0.1 liter; stroke volume, 5 c.c.; venous pressure, 2 cm.; and circulation time, 2 seconds. The means of the normal group have been extended through the other groups by a dotted line. The mean of each group is indicated by the position of an arrow just below or above that particular group. Figure 2*a* refers to data of hypertensive, arteriosclerotic and syphilitic patients (miscellaneous group), before, during, and after recovery from heart failure; figure 2*b* refers in a similar fashion to rheumatic heart disease; and in figure 2*c* the data from figure 1*a* and 1*b* are combined.

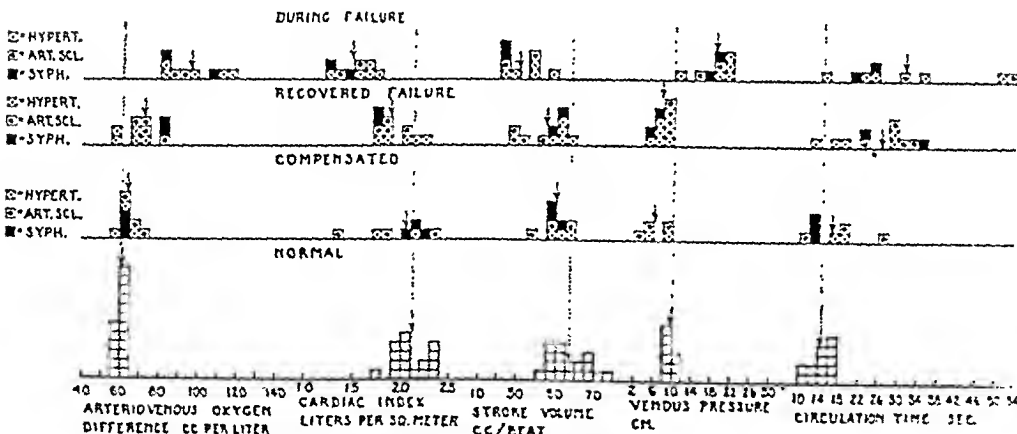
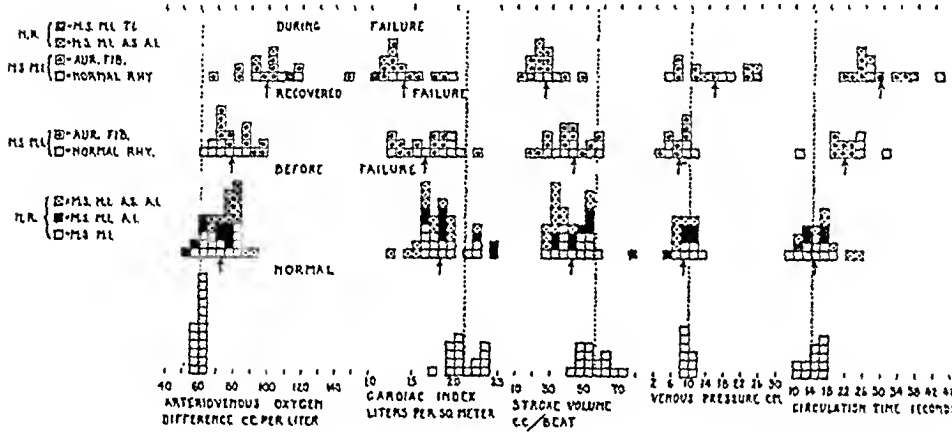
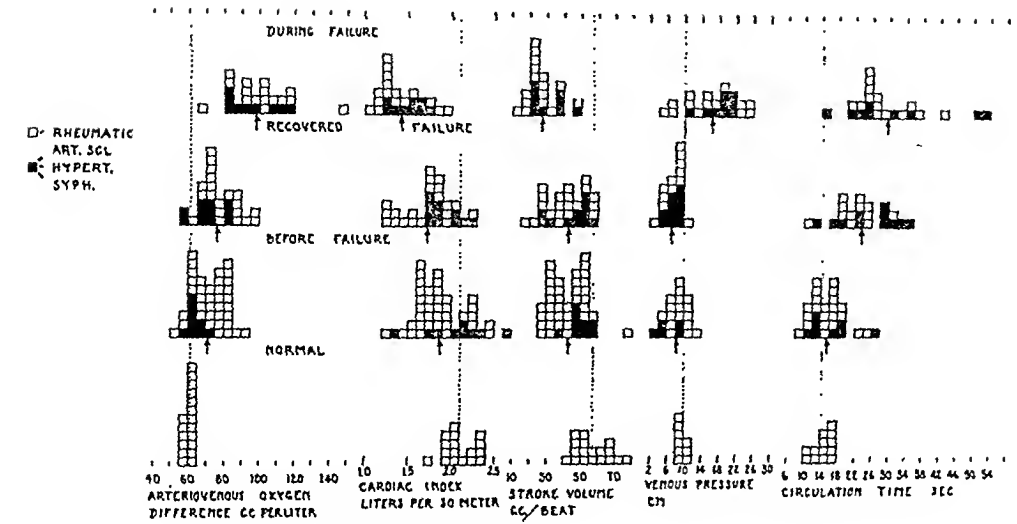


FIG. 2.

TABLE III

Data Relating to Patients Who Have Recovered from Heart Failure

Name	Age	Sex	Date	Oxygen Consumption	Arterio-venous Oxygen Difference	Cardiac Output	Cardiac Output	Heart Rate	Stroke Volume	Arterial Pressure
				c.c. per min.	c.c.	l./min.	l./sq.m./min.	per min.	c.c.	mm.Hg
<i>Hypertensive Group</i>										
A. F.	38	M	1/15/36	203	59.6	3.41	2.20	70	49	205/128
M. R.	38	M	1/29/36	207	68.0	3.04	1.70	60	50	170/80
M. H.	53	M	12/ 3/35	230	68.9	3.34	2.00	64	52	148/98
			12/11/35	220	70.9	3.10	1.84	60	52	148/95
L. B.	64	M	3/ 6/36	216	59.2	3.65	2.11	66	55	212/100
<i>Arteriosclerotic Group</i>										
C. K.	48	M	10/25/35	218	69.6	3.13	2.02	112	28	106/74
			11/18/35	207	72.8	2.84	1.81	100	28	106/58
			11/21/35	209	73.9	2.83	1.85	96	30	104/80
F. St. J.	73	M	10/ 2/35	241	81.2	3.00	1.70	66	45	136-130/80
<i>Luetic Group</i>										
F. V.	50	M	3/ 3/36	235	83.9	2.80	1.71	54	52	166/54
W. E.	42	M	3/24/36	234	81.3	2.88	1.74	62	46	180/90
<i>Rheumatic Group</i>										
S. S.	32	M	2/24/36	236	74.3	3.20	1.90	58	55	105/58
W. B.	32	F	5/ 7/36	166	82.3	2.02	1.50	48	42	98/65
F. S.	24	M	4/13/35	195	64.6	3.02	1.91	72	42	106/66
M. R.	32	F	4/ 4/34	158	89.6	1.76	1.21	60	29	115/55
C. W.	25	M	12/ 7/35	290	73.4	4.00	2.03	70	57	102/54
			12/19/35	286	75.8	3.77	1.95	70	54	116/66
L. A.	24	F	5/11/34	179	68.6	2.61	1.64	70	37	95/60
			5/31/34	194	65.5	2.95	1.80	93	32	120/84
J. G.	28	M	3/25/35	247	74.1	3.33	2.22	60	56	134/65
J. G.	28	M	11/12/35	237	86.3	2.75	1.80	66	42	135/76
			11/16/35	226	86.2	2.61	1.70	50	52	152/76
L. C.	30	F	3/ 6/35	207	74.4	2.78	1.70	70	40	118-110/74
M. C.	53	F	2/14/36	193	77.8	2.48	1.55	70	35	150/70
G. MacF.	57	M	2/29/36	182	70.8	2.57	1.70	68	38	118/62
M. P.	41	F	5/10/34	159	74.3	2.14	1.40	59	36	100/70
M. R.	25	F	4/11/34	191	96.2	1.98	1.30	86	23	98/60
			4/20/34	180	98.2	1.83	1.20	106	17	98/60
J. W.	28	M	3/ 9/34	188	92.0	2.05	1.34	74	28	115/80
			3/12/34	171	88.0	1.95	1.27	69	29	115/80
A. C.	32	M	4/ 2/35	263	78.3	3.36	1.86	72	47	114/76

\* The cardiac volume has been multiplied by the constant in Bardeen's formula.

† In this column the following abbreviations are used:

Rh = rheumatic fever

Unk. = unknown

Hyp. = hypertension

Artscl. = arteriosclerosis

M.S. = mitral stenosis

M.I. = mitral insufficiency

A.S. = aortic stenosis

A.I. = aortic insufficiency

Enl.Ht. = enlargement of the heart

Syph. = syphilis

R-I-V-HB = right intraventricular heart block

‡ 0, +, ±, ↓, ↑, = absent, present, doubtful, decreased, increased, respectively.

TABLE III (Continued)

Data Relating to Patients Who Have Recovered from Heart Failure

Left Ven-tricular Work	Cir-culation Time	Ve-nous Pres-sure	Vital Ca-pac-ity	Cardiac Area	Cardiac Vol-ume *	Diagnosis †	Signs ‡						Rhythm
							Dyspnea	Cyanosis	Râles	Liver	Edema	Fluid in chest	
gm.m./per beat	sec.	cm.	c.c.	sq.cm.	c.c.								
<i>Hypertensive Group</i>													
111.0	12.5	8.5	2450	128.3	703	Hypert.; Enl.Ht.	0	0	0	±	0	0	N.R.
85.0	19.2	7.9	2800	150.8	894	Artscl.; Enl.Ht.; Hypert.	0	0	0	0	0	0	N.R.
87.0	29.1	6.4	2850	196.0	1325	Artscl.; Hypert.; Enl.Ht.; R-I-V-HB	0	0	0	0	0	0	N.R.
86.0	29.0	7.0	2950	196.7	1331		0	0	0	?	0	0	N.R.
116.0	16.4	5.0	1900	125.9	682	Artscl.; Hypert.; Enl.Ht.	±	0	+	0	0	0	N.R.
<i>Arteriosclerotic Group</i>													
34.0	22.7	9.4	2900	155.3	940	Artscl.; Enl.Ht.	0	±	0	+	0	0	N.R.
32.0	30.4	8.7	2800	160.4	972		0	0	0	0	0	0	N.R.
37.0	28.0	9.4	3050	172.1	1091		0	0	0	±	0	0	N.R.
65.5	33.0	8.0	1800	157.1	951	Artscl.; Enl.Ht.	±	±	±	±	±	0	A.F.
<i>Luetic Group</i>													
77.8	35.5	5.0	3300	182.0	1185	Syph.; A.I.; Enl.Ht.	0	±	±	±	0	0	N.R.
84.5	22.0	6.1	2900	172.4	1094	Syph.; A.I.; Enl.Ht.; Aneurysm	0	±	0	±	0	0	N.R.
<i>Rheumatic Group</i>													
61.0	31.7	5.8	3450	172.9	1097	Rh.; M.S. and M.I.; Enl.Ht.	0	0	0	+	0	0	N.R.
47.0	24.0	5.3	2100	183.4	1198	Rh.; M.S. and M.I.; Enl.Ht.	0	0	0	0	0	0	N.R.
49.0	11.5	9.5	4400	162.9	1005	Rh.; M.S. and M.I.; Enl.Ht.	0	0	0	0	0	0	N.R.
34.0			2100	154.4	925	Unk.; M.S. and M.I.; Enl.Ht.	±	+	0	0	±	0	N.R.
60.5	24.0	10.5	3850	273.6	2185	Unk.; M.S. and M.I.; Enl.Ht.	0	0	0	0	0	0	N.R.
66.8	25.2	8.8	4100	273.2	2185		0	+	0	0	0	0	N.R.
39.2			2700	140.6	806	Rh.; M.S. and M.I.; Enl.Ht.	±	±	±	±	±	0	N.R.
44.4			2610	137.7	781		±	±	±	±	±	0	N.R.
76.2	19.5	8.1	3250	146.5	856	Unk.; M.S. and M.I.; Enl.Ht.	0	0	0	0	0	0	A.F.
60.5	19.9	9.1	2750	154.3	926	Unk.; M.S. and M.I.; Enl.Ht.	0	+	0	+	0	0	A.F.
80.6	22.1	6.3	2900	143.5	821		0	+	0	0	0	0	A.F.
53.9	20.2	6.4	2700	185.3	1218	Rh.; M.S. and M.I.; Enl.Ht.	0	0	0	0	0	0	A.F.
52.3	22.2	8.1	2000	168.7	1160	Rh.; M.S. and M.I.; Hypert.; Enl.Ht.	0	0	0	0	0	0	A.F.
46.5	19.7	2.9	1850	143.1	827	Rh.; M.S. and M.I.; Enl.Ht.	0	0	±	0	0	0	A.F.
41.6			2200	162.0	996	Rh.; M.S. and M.I.; Enl.Ht.	0	0	±	0	0	0	A.F.
24.7			2100	189.8	1271	Rh.; M.S. and M.I.; Enl.Ht.	±	±	±	±	±	0	A.F.
18.5			2310	194.4	1310		±	±	±	±	±	0	A.F.
37.3			2400			Unk.; M.S. and M.I.	±	±	±	±	±	0	A.F.
38.7			2270				±	±	±	±	±	0	A.F.
60.7	18.0	4.7	4350	154.9	932	M.S.; M.I.; A.I.; Enl.Ht.	0	0	0	0	0	0	A.F.

The average output per beat (stroke volume) was decreased to 27 c.c., being 25 c.c. and 30 c.c. respectively when separated into the rheumatic and miscellaneous groups (average normal, 59 c.c.).

The average venous pressure for all groups was increased to 16.2 cm., and was 15.0 cm. and 18.1 cm. respectively in the rheumatic and miscellaneous groups (normal value, 10.1 cm.).

The average circulation time was 29.6 sec., the average normal for this method being about 14.4 sec.

TABLE IV

Data Relating to Cardiac Patients Who Had Never Experienced Heart Failure

Name	Age	Sex	Date	Oxygen Con- sumption	Arterio- venous Oxygen Difference	Cardiac Output	Cardiac Output	Heart Rate	Stroke Volume	Arterial Pressure
				c.c. per min.	c.c.	l./min.	l./sq.m./min.	per min.	c.c.	mm.Hg
<i>Hypertensive Group</i>										
C. C.	44	F	12/ 5/34	270	56.9	4.74	2.69	80	59	234/150
F. E.	50	M	10/22/36	226	69.6	3.25	1.70	64	51	174/130
E. L.	22	M	2/14/34	244	63.1	3.87	2.10	85	46	180/112
<i>Arteriosclerotic Group</i>										
C. McA.	69	M	1/15/35	259	64.6	4.01	2.40	70	57	120/60
J. S.	58	M	10/29/35	160	72.9	2.20	1.38	58	38	122/82
H. C.	50	M	10/ 1/35	267	68.2	3.92	1.84	88	45	120/80
<i>Lutic Group</i>										
H. W.	48	M	10/15/34	227	64.1	3.54	2.02	74	48	118/50
			10/16/34	232	60.3	3.85	2.20	72	53	108/40
			10/17/34	222	60.1	3.69	2.10	74	49	118/46
<i>Rheumatic Group</i>										
J. M.	18	M	1/28/35	218	83.3	2.62	1.68	96	27	110/68
W. L.	20	M	9/29/34	220	76.4	2.88	1.67	74	39	110/80
J. T.	20	M	6/28/34	273	82.4	3.32	1.80	74	45	115/70
W. H.	21	M	2/21/34	240	71.7	3.34	1.65	88	38	122/90
A. G.	23	M	10/30/34	210	69.9	3.00	1.74	76	39	118/80
			11/12/34	214	69.7	3.06	1.79	76	40	118/74
			1/10/35	243	71.9	3.38	1.94	74	46	104/70
			3/28/35	222	61.4	3.62	2.10	74	50	110/70
J. M.	23	M	11/ 3/34	229	81.9	2.97	1.68	72	39	110/60
C. W.	23	M	3/25/36	255	65.2	3.91	2.27	68	57	132/78
A. M.	24	M	9/28/35	203	57.6	3.52	1.90	66	54	124/70
R. T.	29	F	3/14/36	218	61.1	3.57	2.23	66	54	110/58
F. M.	32	M	11/ 1/34	259	81.4	3.18	1.77	70	45	122/72
M. H.	39	F	3/28/34	170	63.7	2.67	1.81	80	33	108/70
A. D.	17	M	11/14/36	218	75.0	2.91	1.80	54	54	125/68
R. L.	21	M	4/ 6/35	234	70.9	3.30	1.89	74	45	120/64
P. H.	22	M	5/22/34	227	64.7	3.51	2.21	70	50	122/74
A. M.	23	F	2/14/35	203	62.7	3.24	1.87	74	44	112/56
A. B.	23	M	4/10/34	207	74.9	2.88	1.63	90	32	136/88
J. L.	25	M	4/19/34	238	77.8	3.06	1.82	100	31	100/62
F. R.	26	M	1/26/34	219	77.5	2.83	1.62	72	40	130/64
H. W.	29	M	1/ 4/35	238	57.9	4.18	2.43	80	52	128/60
H. C.	40	M	6/15/35	249	52.4	4.73	2.40	60	79	108/68
H. N.	14	M	2/ 6/34	232	86.4	2.68	1.93	94	29	138/32
E. C.	19	F	3/18/35	195	82.8	2.36	1.42	86	27	104/10
J. H.	20	M	4/11/34	253	80.8	3.12	1.75	80	39	166/50
			4/15/34	251	90.0	2.80	1.50	83	34	162/40
			4/18/34	234	81.9	2.86	1.60	84	34	152/40
E. P.	21	M	11/ 8/34	195	71.4	2.73	1.77	80	34	122/50
J. F.	25	F	5/18/35	122	65.9	1.85	1.25	70	26	104/50
J. C.	28	M	12/ 9/37	331	75.5	4.15	2.21	80	52	128/30
E. F.	29	M	6/22/34	253	84.7	2.99	1.90	94	32	130/30
J. O.	31	M	3/ 7/36	203	77.7	2.61	1.61	60	44	96/70
M. S.	33	M	6/ 6/34	235	67.8	3.47	1.97	64	54	108/60
I. G.	43	M	6/27/34	249	79.0	3.15	1.87	93	34	155/35
S. H.	45	M	1/ 3/35	218	81.5	2.67	1.57	84	32	86/72
M. C.	46	F	12/10/34	182	77.4	2.35	1.63	66	36	128/84

\* The cardiac volume has been multiplied by the constant in Bardeen's formula.

† In this column the following abbreviations are used:

Rh. = rheumatic fever

Unk. = unknown

Hyp. = hypertension

M.S. = mitral stenosis

M.I. = mitral insufficiency

A.S. = aortic stenosis

A.I. = aortic insufficiency

Enl.Ht. = enlargement of the heart

sl. E.H. = slight enlargement of the heart

Artscl. = arteriosclerosis

I-V-HB = intraventricular heart block

R-I-V-HB = right intraventricular heart block

N.R. = normal rhythm

A.F. = auricular fibrillation

I, IIA, IIB, III, refer to functional classification (Criteria for the Classification and Diagnosis of Heart Disease, ed. 2, New York Tuberculosis and Health Association, New York, 1929).

‡ Roentgen-Rays not repeated on these days.

TABLE IV (Continued)

Data Relating to Cardiac Patients Who Had Never Experienced Heart Failure

Left Ven-tricular Work	Cir-culation Time	Ve-nous Pres-sure	Vital Ca-pac-ity	Cardiac Area	Car-diac Vol-ume *	Diagnosis and Rhythm †
gm.m. per beat	sec.	cm.	c.c.	sq.cm.	c.c.	
<i>Hypertensive Group</i>						
145.1	19.0	5.5	2600	176.3	1130	Hypt.; J-V-HB; N.R.
105.4	17.0	8.0	4450	137.0	774	Hypt.; N.R.
91.3			5640	111.2	566	Hypt.; nephritis; N.R.
<i>Arteriosclerotic Group</i>						
70.0	11.5	5.5	2700	107.7	546	M.I.; not Enl.Ht.; IIA; N.R.
53.0	27.0	3.7	2600	139.0	792	None; not Enl.Ht.; IIA; N.R.
61.2	18.5	8.3	3300	159.3	972	Artscl.; Enl.Ht.; IIA; A.F.
<i>Lutic Group</i>						
55.0	13.2		4100			A.I.; Enl.Ht.; I; N.R.
53.0	13.8		4100	137.5	774	
55.0	12.8		4250	138.5	782	
<i>Rheumatic Group</i>						
32.7	11.0	7.5	3500	111.2	566	Unk.; M.S. and M.I.; I; N.R.
50.4			3400	108.6	542	Rh.; M.S. and M.I.; IIA; N.R.
56.9			4900	114.7	594	Unk.; M.S. and M.I.; ? sl.E.H.; I; N.R.
54.7			4050	114.8	595	Rh.; M.S. and M.I.; I; N.R.
53.0	16.0		4200	144.0	832	Rh.; M.S. and M.I.; Enl.Ht.; I; N.R.
52.0	18.5		4300	141.9	811	
46.7	16.5	11.0	4200	137.7	781	
61.2	15.4	10.3	4200	136.8	772	
45.1	13.2		3700	128.2	701	Rh.; M.S. and M.I.; sl.E.H.; IIA; N.R.
81.4	14.4	8.6	4200	122.4	655	Rh.; M.S. and M.I.; ? sl.E.H.; I; N.R.
71.2	13.4	12.3	5000	137.7	781	Unk.; M.S. and M.I.; ? E.H.; IIA; N.R.
61.7	9.6	8.0	3000	111.9	553	Rh.; M.S. and M.I.; ? sl.E.H.; I or IIA; N.R.
59.4	14.0		4900	138.2	784	Rh.; M.S. and M.I.; IIA; N.R.
40.3			2690	130.9	724	Rh.; M.S. and M.I.; sl.E.H.; IIA; N.R.
71.2	16.0	5.4	4000	119.5	632	Unk.; M.S. and M.I.; A.I.; ? sl.E.H.; I; N.R.
56.0	17.2	10.5	4100	120.6	647	Rh.; M.I., M.S., and A.I.; Enl.Ht.; I; N.R.
66.6			3400	148.3	872	Rh.; M.S. and M.I.; A.I.; Enl.Ht.; IIA; N.R.
52.0	11.6	10.1	2900	97.6	470	Rh.; M.I., M.S., and A.I.; Enl.Ht.; I or IIA; N.R.
48.7			4650	123.6	667	Unk.; M.S. and M.I.; A.I.; I; N.R.
34.2			3940	135.7	764	Unk.; M.S. and M.I.; A.I.; I; N.R.
52.8			4350	141.1	809	Rh.; M.S. and M.I.; A.I.; Enl.Ht.; I; N.R.
66.5	13.0	8.3	3900	149.1	879	Rh.; M.S. and M.I.; A.I.; sl.E.H.; I; N.R.
94.6	12.8	8.2	4700	127.1	691	Rh.; R-I-V-HB; M.S. and M.I.; A.I.; marked E.H.; IIA; N.R.
33.5			2970	124.1	668	Rh.; M.S. and M.I.; A.S. and A.I.; ? E.H.; IIA; N.R.
21.0	10.7	8.2	2850	106.9	551	Rh.; M.I., M.S., A.I., and A.S.; Enl.Ht.; I; N.R.
57.3			4300	180.0	1178	Rh.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.; IIA; N.R.
46.7			4230	180.0	1178	
44.4			4210	180.0	1178	
40.0	19.5		3100	119.2	629	Rh.; M.I., M.S., A.I., and A.S.; Enl.Ht.; IIA; N.R.
27.0	16.6	6.8	2800	121.6	647	Unk.; M.I., M.S., A.I., and A.S.; Enl.Ht.; I; N.R.
55.9	16.4	7.6	4000	113.0	580	Rh.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.; I; N.R.
34.8			3100	247.6	1882	Rh.; M.S. and M.I.; A.S. and A.I.; marked E.H.; IIA; N.R.
49.7	22.9	7.3	2500	170.8	1080	Rh.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.; IIA; N.R.
61.7			3625	164.2	1015	Rh.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.; IIA; N.R.
43.9			3700	168.6	1055	Rh.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.; IIA; N.R.
34.4	25.0	10.2	2450	151.5	899	Unk.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.; IIA; N.R.
52.0	15.6	6.7	2600	125.8	678	Rh.; M.I., M.S., A.I., and A.S.; Enl.Ht.; IIA; N.R.



There was no significant difference in any of the measurements in the four etiological groups during heart failure (figures 1 *a, b, c*).

#### OBSERVATIONS MADE AFTER RECOVERY FROM HEART FAILURE

There are 31 observations on 23 subjects. The average cardiac index was decreased to 1.73 liters (normal 2.09 liters), the average decrease being greater in the rheumatic group than in the miscellaneous group (tables 2 and 3; figures 2 *a, b, c*).

The average arteriovenous oxygen difference was increased to 76.9 c.c. (normal 61.5 c.c.), the average stroke volume decreased to 44 c.c. (normal, 59 c.c.); the average venous pressure was 7.3 cm. (normal range), and the circulation time was prolonged to 23.7 sec. (normal, 14.4 sec.). There were no marked differences in the etiological groups.

#### OBSERVATIONS MADE BEFORE THE OCCURRENCE OF HEART FAILURE

There are 46 observations on 39 patients. The average cardiac index was reduced to 1.87 liters (normal, 2.09 liters; tables 2 and 4; figures 2 *a, b, c*), the average arteriovenous oxygen difference increased to 71.4 c.c. (normal, 61.5 c.c.), the stroke volume decreased to 43 c.c. (normal, 59 c.c.), the average venous pressure was 8.1 cm. (normal range), and the circulation time 15.4 sec. (normal range).

#### DISCUSSION

These data show that in the presence of congestive heart failure there is marked decrease in the functional capacity of the heart in that it pumps less blood per square meter of body surface per minute than does a normal heart, that the output per beat is decreased, that the blood consequently circulates at a reduced velocity, shown by the prolongation of the circulation time, and that there is usually rise in venous pressure. The arteriovenous oxygen difference is increased.

Patients who have organic heart disease but have not suffered failure show, on the average, a slight decrease in cardiac index and output per beat, increase in arteriovenous oxygen difference but no significant change in circulation time and venous pressure.

On the other hand, patients who have recovered from congestive heart failure show values intermediate between those exhibiting failure and those who have never experienced failure; that is to say, the cardiac index is greater than during failure but not as near normal levels as before heart failure occurred. The circulation time is prolonged but shorter than during failure.

It appears, therefore, that during failure the heart is less effective as a pump than it is in a normal individual and less effective than a heart that is damaged by organic heart disease but has not been subjected to failure, and

also less effective than is an organically diseased heart after it has recovered compensation.

These changes are not associated with alterations in basal metabolic rate. The average progression appears to be slight decrease in cardiac output per beat and per minute in patients exhibiting organic heart disease before the occurrence of failure, a greater decrease in those recovered from failure, and a still greater decrease in the presence of congestive heart failure. This trend is illustrated further in the case of those patients studied both during failure and after return to compensation (tables 1 and 3; figure 3), since in them cardiac output per minute and per beat is less during failure than after compensation has been restored. These results are in agreement with those recorded by Stewart and Cohn,<sup>1</sup> Stewart, Deitrick, Crane, and Wheeler<sup>3</sup> and Stewart, Deitrick, Watson, Wheeler, and Crane.<sup>14</sup> The observations of McGuire, Shore, Hauenstein, and Goldman<sup>15, 16</sup> point to similar conclusions. Harrison, Friedman, Clark, and Resnik,<sup>17</sup> however, were of the opinion that "the level of the cardiac output per minute, whether considered as such or in relation to the metabolic rate, bears no relation to the presence or absence of congestive failure." McGuire<sup>15</sup> has analyzed the discrepancy between Harrison's results and his, and we have already discussed differences between Harrison's results and ours.<sup>3</sup> Our observations confirm the notion expressed in our earlier papers<sup>1, 3, 14</sup> and lend support to the opinion arrived at by Altschule<sup>18</sup> in his excellent analysis of the data which were available at that time, namely that "the fundamental defect (in congestive heart failure \*), however, is a cardiac output which, in relation to the metabolic requirements of the body and to the venous return, is abnormally lowered."

The heart size was larger during failure than after recovery from failure in those in whom the comparison was possible (tables 1 and 3), a finding to which Stewart and Cohn<sup>1</sup> and Stewart, Deitrick, Crane and Wheeler<sup>3</sup> have already directed attention. The work of the left ventricle per beat in its relation to heart size has been studied with respect to the functional state of the patients (tables 1, 3 and 4; figure 4). Stewart and Cohn<sup>1</sup> expressed the opinion that the explanation of increase in cardiac output with decrease in cardiac size as a consequence of giving digitalis was to be found in Starling's<sup>19</sup> "law of the heart." Starr and his associates<sup>11, 20</sup> have presented data since then showing that this "law" applies to basal cardiac work in human beings as well as to that in heart-lung preparations, since they found that the work of the left ventricle which is maintaining an adequate circulation bears a linear relation to the size of the heart. From their data, they defined a zone of normal circulatory function. In a manner similar to theirs, we have plotted cardiac volumes as abscissae and grammeters of work of the left ventricle per beat as ordinates (tables 1, 3 and 4; figure 4). During heart failure (figure 3 *d* and *e*), the values for all except two patients

\* Parenthetical statement introduced by H. J. S. to carry over the context of the preceding sentence.

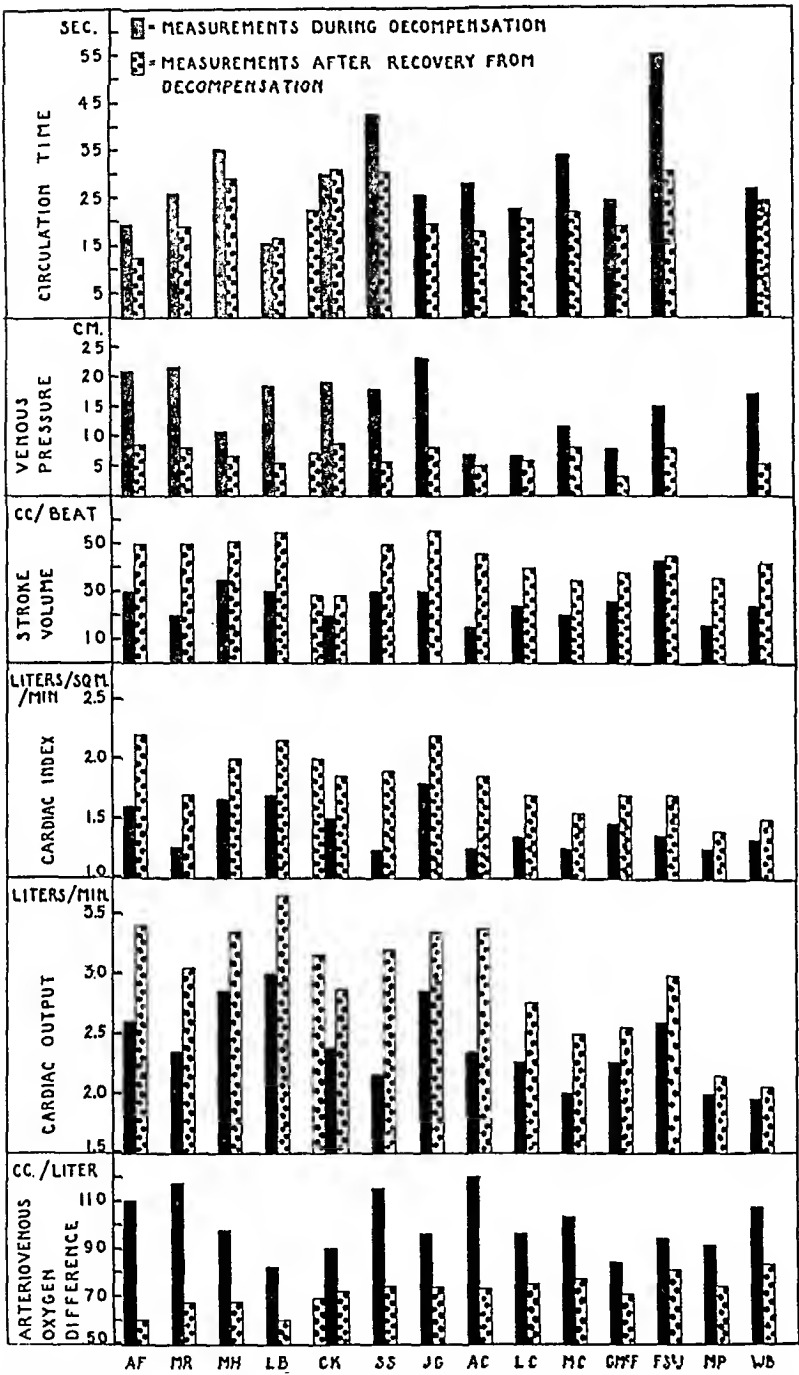


FIG. 3. In this figure are plotted data from tables 1 and 3 relating to patients studied during cardiac decompensation and again after recovery from failure.

fell outside and below line CD, in an area, indicating that in them the work of the heart was not commensurate with size. In those recovered from failure (figure 4 c and e), a greater number were inside the normal zone, and others have moved closer to line CD; in short, they were not so far outside the normal zone. On the other hand, in those patients suffering from heart

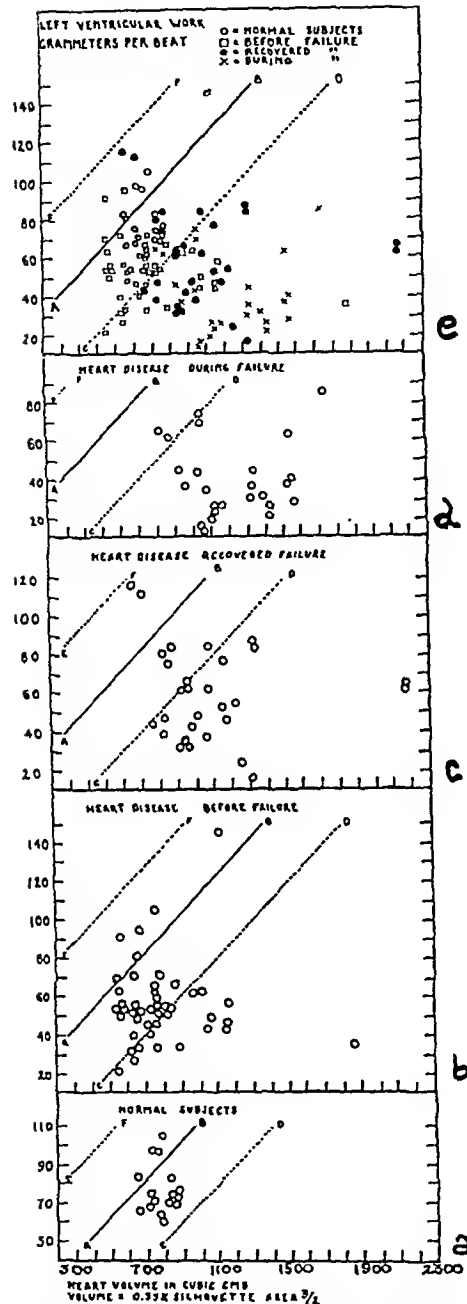


FIG. 4. Left ventricular work per beat and cardiac volume. The data from tables 1, 3 and 4 relating to work of the left ventricle per beat in patients suffering from heart disease are plotted against the corresponding cardiac volumes. Line *AB* represents the best line, the regression of the work on area, defined by Starr, Collins, and Wood on the basis of a statistical treatment of data from a control group of cases. Lines *CD* and *EF* are placed by these authors at a distance of twice the standard deviation from *AB*. It appears from their observations that a patient falling within zone *CD-EF* has a normal circulatory function; that is to say, the work of the heart is commensurate with its size. On the other hand, they found that the values relating to patients who had suffered from cardiac decompensation fell in a zone below *CD*. Each symbol represents a measurement in the group as indicated. In figure 4*b* are data relating to measurements made of cardiac patients before the occurrence of failure; in figure 4*c*, data in those recovered from failure; and in figure 4*d* data collected during heart failure. In figure 4*a* are given normal data for comparison. In figure 4*e*, the data from figure 4, *a*, *b*, *c*, *d* are plotted on one chart for comparison.

disease who had never experienced failure, most fall in the normal zone, and a few who fall below line CD take a closer position on the whole than those in failure and those recovered from failure (figure 4 *b* and *c*). In those studied in both states, failure and compensation, arrows indicate their improved position on the chart with return to compensation (figure 5).

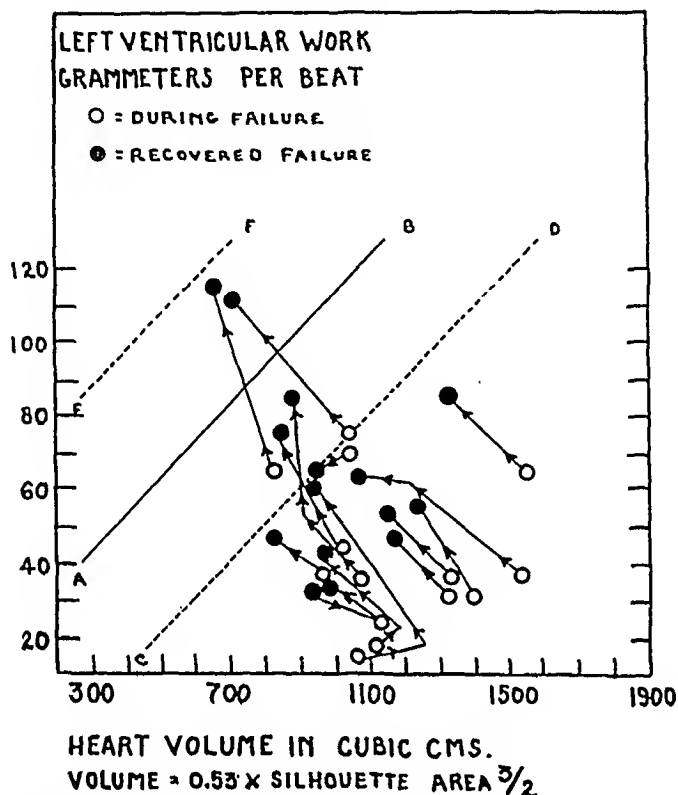


FIG. 5. Left ventricular work per beat and cardiac volume. The data of tables 1 and 3 relating to work of the left ventricle per beat are plotted against cardiac volume in those patients in figure 3 in whom observations were made during failure and again after recovery, in a manner similar to figure 4. Arrows indicate the shift in position on the diagram with return to compensation.

The spread of data in the frequency charts (figure 2 *a*, *b*, *c*) shows overlapping of values in the different clinical functional states. This is not unexpected, since not only the extent of valvular and myocardial damage differs from patient to patient, but also individual variations in the adjustments of the circulatory apparatus and of the organism as a whole are to be expected.

In the light of our observations, heart failure does not appear to fall into the categories of "right-sided" or the "left-sided" variety, nor do the concepts of "backward" failure or "forward" failure appear to us to explain heart failure as it is most frequently encountered in the clinic. The general use of these terms when applied to heart failure gives rise to sureness which the facts do not warrant, and from these labels arises a security which acts as a deterrent to further progress in the understanding of the mechanism of heart failure.

## SUMMARY

Certain circulatory measurements have been made of patients exhibiting organic heart disease of the four common etiological types, namely rheumatic, arteriosclerotic, hypertensive, and syphilitic. It appears that:

(1) Organic heart disease in patients who have not experienced failure is associated with decrease in cardiac index and in cardiac output per beat.

(2) The cardiac output per minute and cardiac output per beat are decreased further in the presence of congestive heart failure.

(3) As compensation is restored, there is increase in cardiac index and in cardiac output per beat. The values do not usually, however, achieve the level prevailing before the occurrence of failure; they take a position intermediate between those made during failure and those made in patients who have never experienced failure.

(4) The venous pressure is usually elevated in congestive heart failure.

(5) The average circulation time is prolonged in patients suffering from congestive heart failure and in those recovered from failure, but the average value is normal in those who have not experienced failure.

(6) The arteriovenous oxygen difference is increased slightly in organic heart disease, more after recovery from failure, and still more in the presence of heart failure.

(7) The work of the heart per beat in relation to its size may be normal or show slight decrease in the presence of heart disease before failure occurs. In the presence of heart failure, there is a marked discrepancy between the size of the heart and the work, so that the values fall outside the zone of normal circulatory function. After recovery, the heart size-work relationship is restored toward the normal level so that the position on the chart moves closer to or into the normal zone.

## CONCLUSIONS

There is marked decrease in the functional capacity of the heart as a pump in congestive heart failure as shown by the decrease in cardiac output per minute per square meter of body surface (cardiac index) and per beat; prolongation of the circulation time occurs, as also may rise in venous pressure. Moreover, the size of the heart increases. Since the output per beat is decreased, and the heart size is larger, the work per beat is no longer commensurate with the size of the heart. With restoration of compensation the functional capacity is increased toward a normal level but on the average does not attain the level of which it was capable before the onset of failure.

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# CASE REPORTS

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## HEMOCHROMATOSIS: REPORT OF A CASE IN WHICH TUBERCULOUS PERITONITIS WAS A COMPLICATION \*

By CARL G. MORLOCK, M.D., F.A.C.P., *Rochester, Minnesota*

HEMOCHROMATOSIS is a disease of infrequent occurrence. Sheldon, in 1935, accepted a total of 311 reported cases as genuine. Butt and Wilder have added 30 cases which were observed at The Mayo Clinic in 15 years. Stewart emphasized the rarity of the disease by showing that its incidence was 0.136 per cent in the necropsies performed in the British hospitals. Althausen and Kerr determined that the incidence of the disease varied from 0.003 per cent among 106,000 patients who were admitted to Johns Hopkins Hospital to 0.005 per cent among 60,000 patients who were admitted to the University of California Hospital. The disease has a remarkable age incidence: in most cases the patients are between 45 and 55 years of age. There is an unusual predominance of the disease among men. Sheldon found only 13 authentic instances of the disease among females, and in the series of cases reported by Butt and Wilder only one patient was a female.

There are many other remarkable features of this disease which have induced Sheldon to name it a "key disease" and to make a plea for a most intimate study of the condition. It is because of these facts and the unusual features in a case observed at the clinic that I have been prompted to consider it worthy of record.

### CASE REPORT

A white man, aged 54, sought advice at the clinic because of abdominal pain and ascites. He had been in excellent health all of his life except for the usual diseases of childhood and an elevated blood pressure, which had been discovered a year before he came to the clinic. He was an electrical engineer and had never been exposed to poisoning by any of the heavy metals. On close inquiry his wife volunteered that eight years before the patient came to the clinic she had noted a darkening of the skin of his face and hands, which she had attributed to excessive exposure to sunlight. Three months before his admission he had had a sore throat, high fever and delirium. During a slow convalescence he had suffered from dull, persistent pain in the lower part of the abdomen. Loss of strength had become pronounced and cardiac and respiratory embarrassment had developed as a result of progressively increasing abdominal distention.

When the patient was examined at the clinic he obviously was ill. His temperature was 100° F., the pulse rate was rapid, and there was evidence of orthopnea. The abdomen was tender and filled with fluid. The edge of the liver was palpable 4.5 cm. below the costal margin. The most striking feature was the dusky, cyanotic, grayish-brown color of the face. The skin was dry; there was a definite brown metallic pigmentation of the hands, forearms and legs; this was visible to a lesser extent on the remainder of the body. The palmar creases were sharply defined by a brownish melanin-like pigmentation. The buccal mucosa was free of pigment, but

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it and the tongue were smooth and cherry red in color. The pigmentation resembled most closely that of Addison's disease, although it was not entirely characteristic of this condition. There was in addition a slight scleral icterus. The genitalia were atrophic; the prostate gland was soft and small.

The patient was admitted to the hospital for observation. He had an intermittent fever which reached a peak of 104° F. A salt-free, low-protein, high-carbohydrate diet, the oral administration of ammonium nitrate, the intravenous administration of a concentrated solution of d-glucose and salyrgan did not enable the patient to maintain a favorable water balance. The abdominal distention increased in amount. A diagnostic and therapeutic abdominal paracentesis was performed and 7000 c.c. of straw-colored fluid were removed. The fluid contained a few erythrocytes and leukocytes; the concentration of total protein was 3.74 gm. per 100 c.c. A special search did not reveal any acid-fast bacilli or malignant cells in this fluid. The high concentration of protein in the ascitic fluid indicated that it was not a simple transudate but an accumulation of fluid caused by an intraabdominal inflammatory process.

The urine was normal except for a slight reduction of Benedict's reagent by several specimens. The flocculation test for syphilis was negative. The concentration of hemoglobin was 14.6 gm. per 100 c.c. of blood; the erythrocyte count and the leukocyte count were 4,220,000 and 10,700, respectively, per cubic millimeter of blood. The differential blood count disclosed 91 per cent neutrophils and a definite macrocytosis. The concentration of urea varied between 22 and 46 mg. per 100 c.c. of blood. On three different occasions the values for the fasting blood sugar were reported as 113, 120 and 91 mg. per 100 c.c. The concentration of serum bilirubin was 2.8 mg. per 100 c.c. and the Van den Bergh reaction was direct. A bromsulphthalein function test disclosed retention, grade 3. The concentration of plasma chloride was 562 mg. per 100 c.c.; the concentration of serum sodium was 296 mg. per 100 c.c.; the concentration of serum potassium was 19.7 mg. per 100 c.c.; the concentration of plasma cholesterol was 88 mg. per 100 c.c.; the concentration of plasma cholesterol esters was 44 mg. per 100 c.c.; the concentration of plasma lecithin was 147 mg. per 100 c.c., and the concentration of plasma lipoids was 255 mg. per 100 c.c. The value for serum protein was 7.9 gm. per 100 c.c. and the albumin-globulin ratio was 1:1.7. The colloidal osmotic pressure of the blood was 293 mm. of water. The sedimentation rate of the erythrocytes was 86 mm. at the end of one hour. Spectroscopic examination of the blood did not disclose any abnormality. Cultures of the blood on blood agar and brain broth did not produce any growth in 48 hours. A roentgenogram of the thorax revealed old healed tuberculous lesions in the apices of both lungs.

On the basis of the pigmentation of the skin, the demonstrable injury of the liver, the borderline level of the concentration of blood sugar, and the macrocytosis, a diagnosis of hemochromatosis with cirrhosis of the liver was made. The cause of the peritoneal exudate was not evident. The patient did not respond to therapeutic measures but his condition became rapidly worse than it had been. Bronchopneumonia and thrombosis of the right femoral vein developed and the patient died.

Necropsy disclosed that the peritoneal cavity contained 800 c.c. of yellow purulent fluid. There were many adhesions and the parietal and visceral portions of the peritoneum were covered with a reddened granular exudate and were studded with multiple discrete and confluent nodules. Microscopic examination disclosed that these nodules were tubercles. Healed tuberculosis was found in the apices of both lungs; the hilus nodes were involved in an active caseating tuberculous process. The heart weighed 403 gm.; the spleen weighed 370 gm. (normal weight 200 gm.), and the liver weighed 2648 gm. (normal weight 2000 gm.). The liver was a dark bronze color; its surface was nodular and hobnail in type; the cut surface was firm and colored brown. In addition to that of the skin and liver, there was macroscopic evidence of pigmentation of the pancreas, heart, adrenal glands, thyroid gland, prostate gland and seminal vesicles.

Microscopic examination disclosed a diffuse tuberculous peritonitis that involved the entire parietal and visceral peritoneum. Most marked of all the microscopic findings was the pigmentation which was readily demonstrated to be the result of an iron-containing compound. The pigment was present in great quantity in the liver (figure 1a) where it had permeated the extracellular fibrous tissue and was found in lesser

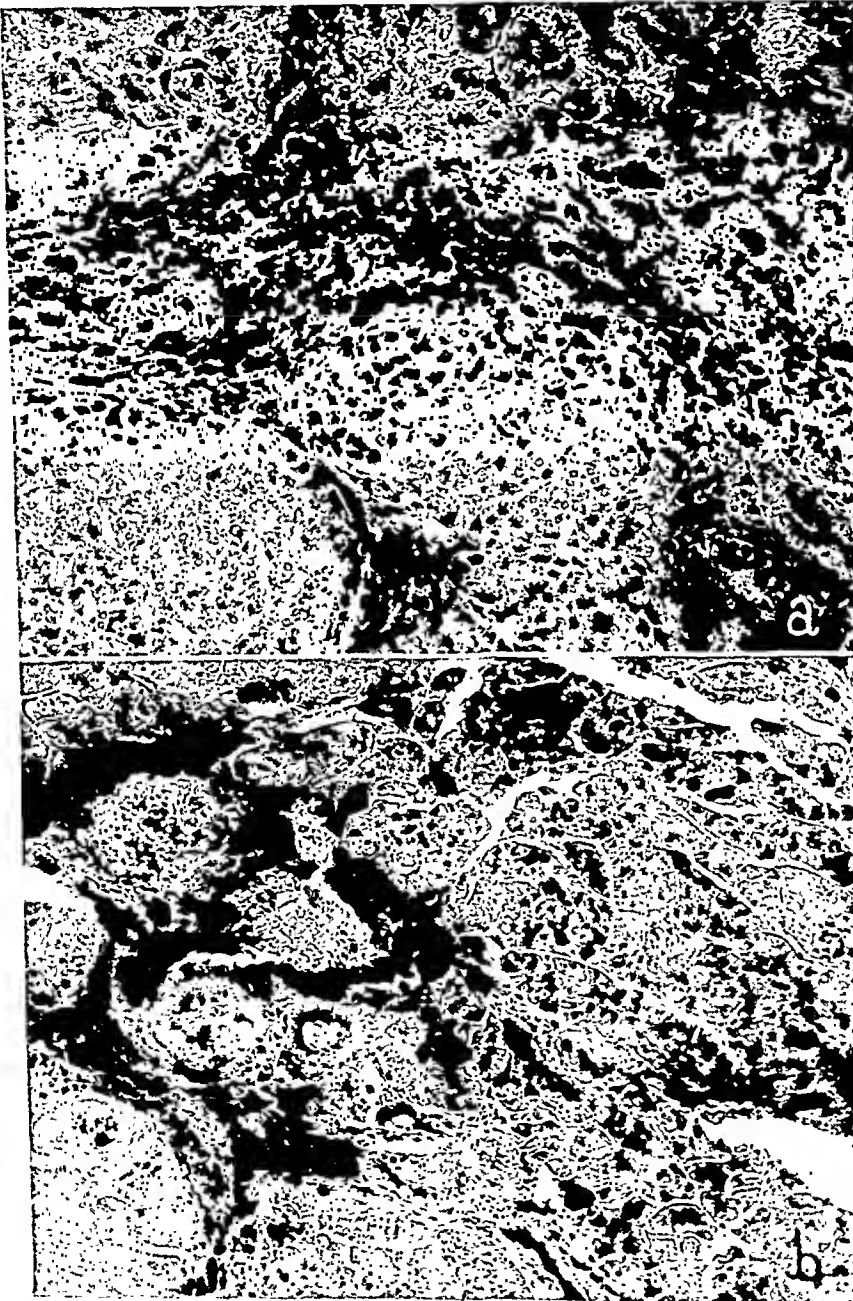


FIG. 1a. Section of liver showing marked cirrhosis; hemosiderin granules are clearly evident in the fibrous tissue stroma but less so in the parenchymal cells; section stained with potassium ferrocyanide and basic fuchsin ( $\times 145$ ); b, section of pancreas showing increase in fibrous tissue and heavy deposits of hemosiderin in the fibrous tissue and in the parenchymal cells; specimen stained with potassium ferrocyanide and basic fuchsin ( $\times 145$ ).

degree in the parenchymal cells. There was a considerable increase of fibrous tissue in the liver and a well-marked cirrhosis. Pigment was extensively deposited in the pancreas (figure 1b), where an increase of fibrous tissue was marked. It is at once evident that although the most extensive deposit of pigment occurred in the extracellular fibrous tissue, much pigment also was deposited in the parenchymal cells both of the islets of Langerhans and the glands of external secretion. In the spleen, iron-containing pigment was present in the pulp cells and fibrous tissue of the trabeculae. Considerable iron-containing pigment also was evident in the mucosal cells of the stomach, in the myocardium (figure 2), in the glandular epithelium of the thyroid,

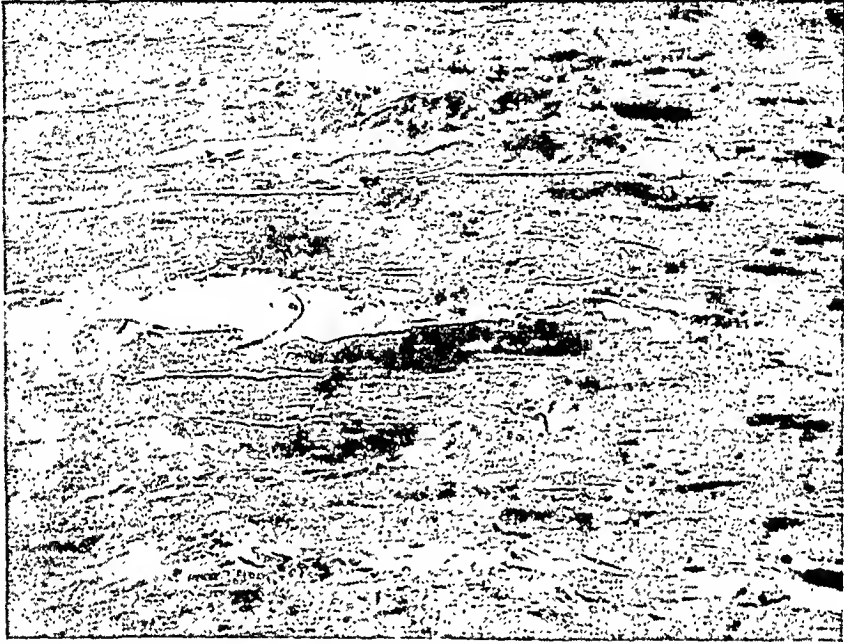


FIG. 2. Section of myocardium showing extensive deposit of dark staining hemosiderin granules in the muscle fibers; section stained with potassium ferrocyanide and basic fuchsin ( $\times 200$ ).

adrenal and prostate glands, and in the interstitial cells of the testes. In the skin, iron-containing pigment was evident in minor degree in the sudoriferous glands. It has been stated that the kidney escapes pigmentation, but in this case pigment was found in isolated portions of the tubular epithelium and to a lesser extent in the glomerular epithelium.

#### COMMENT

*General Features of the Disease.* The first symptoms of this disease, which occur with equal frequency, are diabetes, some abdominal symptom such as pain or visceral enlargement, and pigmentation of the skin. In this case pigmentation of the skin occurred first. Pigmentation occurs in 80 per cent of cases; it usually is bronze or a bluish metallic color which resembles the color of slate. The whole body is usually affected, but it is characteristic that the face, the extensor surfaces of the forearms and the dorsa of the hands are most involved. One striking observation was the occurrence of pigmentation of the buccal mucosa in 16 per cent of cases.

That diabetes is sometimes a late sequela of the disease is suggested by this

case, for although a slight glycosuria was noted in occasional specimens of urine the values for the fasting blood sugar were within the normal range. When diabetes is once established in these cases it often becomes rapidly severe and extremely difficult to control. Sometimes the diabetes is refractory to the use of insulin.

Hepatomegaly and ascites are the most commonly encountered abdominal symptoms. Sheldon found reference to jaundice in only seven cases. In the case that I am reporting there was a definite, though minimal, clinical jaundice and elevation of the concentration of serum bilirubin.

Sexual hypoplasia that is associated with genital atrophy, loss of hair and impotence has been noted. It has been postulated that this is secondary to the glandular dysfunction caused by deposit of pigment in the pituitary body.

Sheldon said that the average duration of the disease is 18.5 months after the first symptom becomes obvious enough to induce the patient to seek medical advice. In the case that I am reporting abnormality of pigmentation had been noted, but had not been considered significant, at least eight years before death.

Tuberculosis was the precipitating cause of death in this case and has been the cause of death in 9 per cent of all cases of hemochromatosis. Diabetes and its complications account for more than half the deaths in cases of this disease.

*Pigmentation.* There are two demonstrable pigments concerned in hemochromatosis. One is hemosiderin, an iron-containing compound, which is believed to be a ferric hydrate of colloidal nature that is loosely bound with fat and protein. This pigment occurs in the secreting cells of the glands of both internal and external secretion; in the connective tissue of these organs; in the lymph nodes; in striated muscle, especially that of the heart; in the reticulo-endothelial system; in the alveolar epithelium of the lungs; in the cartilages and synovia of joints; and occasionally in the walls of blood vessels.

The second pigment, hemofuscin, is found in the epithelial cells of glandular organs; extracellularly in the connective tissue of these organs; in smooth muscle; and most extensively in the walls of the medium-sized and small arteries. Hemofuscin is a pigment which has been described as dark brown, black or yellowish-brown. It does not react to any of the microchemical tests for iron and actually does not contain iron. It is readily stained by the basic aniline dyes and is believed to be related to the melanins.

*Theories of Etiology of the Disease.* Many theories have been advanced to explain the production of this disease. Some men believe that it is due to the destruction of blood and the accumulation of pigment left by the normal wear and tear of the erythrocytes. Diabetes mellitus and cirrhosis of the liver have been cited as primary disturbances responsible for the disease. Toxic factors have been suggested, and in turn bacteriologic toxins, alcohol, zinc, lead, and copper have been eliminated as causative agents.

The idea that the fundamental nature of the disease consists of a disorder of metabolism has much to commend it. The theory which has met the widest acceptance is that the tissues have an abnormal avidity for iron. In general, however, even this explanation is unsatisfactory, its most obvious failing being that it concerns only an explanation for the deposits of hemosiderin; it does not consider the simultaneous deposit of hemofuscin.

The most feasible suggestion for the accumulation of hemosiderin is that there is some abnormality in the removal of iron from the cell in the normal

cycle of entrance and exit; thus there is piled up a useless residuum of iron which eventually bursts and kills the cell which contains it. As a result, the iron is found in an extracellular situation after death. One difficulty in proving this theory is the limitation which clinical methods impose in the evaluation of the metabolism of iron. Dry, as a result of a very carefully balanced experiment, concluded that in cases of hemochromatosis there is not an increased retention of iron as compared to normal. However, it may be argued that the average daily retention needed to accumulate the large amounts of iron in the tissues, is too small to be appreciated by this type of experiment unless it is very prolonged. This theory of the deposit of iron-containing pigment has the disadvantage that striated muscle is relatively unaffected; however, the theory is supported by the fact that as age advances the accumulation of pigment becomes more pronounced and that in really rapidly growing cells, such as cancer cells, there is scant deposition of the pigment.

The deposits of hemofuscin appear to be a part of a disturbance of the metabolism of melanin, which equally with that of iron must be regarded as one of the essential features of hemochromatosis. That one is justified in considering an alteration in the metabolism of melanin as one of the characteristic features of the disease is indicated by the fact that one of the main clinical features, namely pigmentation of the skin, is in all cases largely, and in some cases solely, due to a great increase in the melanin content of the deeper layers of the epidermis. Especially noteworthy is the fact that hemochromatosis has been complicated by melanuria.

The most reasonable explanation of hemochromatosis is that it is due to an inborn error of metabolism which is far more common among males and which at times actually has a familial incidence.<sup>4</sup> The error concerns the inner metabolism of probably all the cells of the body. The production of pigment may be the result of a disturbance of the normal changes in intracellular chemistry which are dependent on the processes of aging of the cell. The hypothesis of an error of metabolism appears to be the only one which will encompass the enormous array of facts provided by the clinical, pathologic and chemical aspects of the disease.

#### COMMENT

The absence of significant clinical diabetes and the presence of jaundice in this case are noteworthy. The pigmentation of the exposed surfaces of the body and of the palmar creases suggested an Addisonian pigmentation rather than hemochromatosis.

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## CHRONIC LEUKOPENIA WITH FATAL TERMINATION DUE TO AGRANULOCYTIC ANGINA; CASE REPORT\*

By ISRAEL KOPP, M.D., *Boston, Massachusetts*

THE literature now contains many case reports of agranulocytosis since its first description by Schultz in 1922.<sup>1</sup> Various hypotheses as to its etiology have been offered, and a number of drugs, nearly all containing the benzene ring, have been implicated.<sup>2, 3, 4</sup>

Agranulocytosis has been defined as a disease in which essentially there is a marked diminution or total absence of the granulocytes of the peripheral blood, which is followed by a loss of cellular resistance as shown by infectious processes of various types.<sup>4</sup> Various other descriptive terms have been given to this syndrome, such as agranulocytic angina, primary granulocytopenia and idiopathic or primary or malignant neutropenia. The term pernicious leukopenia was proposed by Fitz-Hugh<sup>2</sup> in place of those mentioned above to indicate that all the leukocytes were diminished, whereas all other terms emphasized only the most striking feature of the disease, i.e., a marked reduction in the granulocytes.

Cases of recurrent and chronic granulocytopenia or neutropenia have been reported by numerous observers.<sup>5, 6, 7, 8, 9, 10, 11</sup> In the recurrent form the disease is cyclic, acute exacerbations occurring at variable intervals with or without relationship to other factors such as the menstrual flow, drug ingestion, vaccines, etc. The white cell count between recurrences is in some cases within normal limits, with polymorphonuclear neutrophils quantitatively and qualitatively normal, and in other cases reveals for a prolonged period granulocytopenia.

In the chronic form of granulocytopenia the white cell count remains low and ranges from 2500 to 5000.<sup>12</sup> The cells are normal in appearance and percentage relationship. In some patients this low white cell count is accompanied by good health and a normal response to infection. In others, vague symptoms are present and the polymorphonuclear neutrophile response to demands above that normally made on the body (such as an infection) is inadequate.

We wish to report a case of marked leukopenia of at least four and a half years' duration and of unknown etiology, which terminated fatally in agranulocytic angina. Of considerable interest in this patient is the transition of a marked leukopenia with all the white cell elements absolutely, but not relatively, diminished to one of a typical agranulocytic angina.

### CASE REPORT

The patient, D. F., aged 49 years, a married male, a building contractor by occupation, was seen on February 6, 1934, with dizziness the chief complaint. For the past few years he had experienced dizziness, which had been relieved at first by the wearing of glasses, but which of late had become worse. He experienced occasional generalized headaches which resembled those "after a night's drinking" and were relieved somewhat by squeezing the frontal area. He complained also of occasional buzzing and whistling in the ears and insomnia. His memory had become poor. There was some dyspnea on going up an incline, due probably to his obesity. There were shooting rheumatic pains in the left lower extremity and occasional pains in the left knee-joint relieved by exercising the joint.

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From the Boston Psychopathic Hospital.

The patient was an Italian by birth and accustomed to taking about one quart of wine daily.

The past history revealed gonorrhea at the age of 25 with adequate treatment.

Physical examination revealed a tall (71 inches), well nourished, obese patient (weight 225 pounds), with a large protuberant abdomen. Other significant findings were as follows:

The pupils were equal, the right slightly irregular; the reactions to light and accommodation were normal. The tonsils were small, adherent and moderately injected. The heart and lungs were negative. Blood pressure was 145 mm. of mercury systolic and 95 diastolic. Neurological examination was negative except for equally diminished patellar reflexes. The Wassermann reaction of the blood was negative. Urine examination was negative. Lumbar puncture was advised but refused. Results of blood examinations done when the patient was first seen and on subsequent visits are shown in table 1.

Since the patient was quite concerned about his insomnia, 3 grains of sodium amytal were prescribed. This medication was taken on two occasions only. Close questioning revealed that two months before (December 1933) another physician had prescribed a tablet medication of which he took three a day for two weeks. Occasionally the patient had taken potassium iodide, 40 drops daily, as a medication for rheumatism.

From February 6, 1934 to May 12, 1934 the blood was examined on six occasions and on each revealed a marked leukopenia, the various white cell elements being absolutely but not relatively diminished (table 1). The patient's chief complaints during this period were dizziness and insomnia. He was not seen again until January 1938. He had enjoyed very good health in the interim and had gained weight. His chief complaint at this time was abdominal discomfort especially after meals. The hearing of the right ear was impaired and insomnia was still present. He had continued to take one quart of wine daily. The physical examination revealed nothing new. In view of the obesity and the difficulty in palpating the abdomen a roentgen-ray of the abdomen was taken and revealed the following:

"The liver is not well outlined but is probably normal. There is a suggestion of a large mass in the left side of the abdomen which might well be an enlarged spleen and seems definitely too large for kidney."

A roentgen-ray of the chest revealed no pathologic process. Pentnucleotide therapy was advised but was refused by the patient.

The patient was again seen on August 3, 1938. There were no complaints except for some pain in the left knee-joint. He was in good physical condition and had gained 25 pounds in weight. A roentgen-ray of both knee-joints revealed some arthritic changes. A roentgen-ray of the abdomen was interpreted as follows:

"The shadow in the left abdomen thought to be an enlarged spleen is only suggested today and seems rather more like kidney than spleen. Not so large as previously."

A blood examination revealed again a marked leukopenia with 45 per cent polymorphonuclear neutrophils (table 1).

On August 28, 1938 the patient was admitted to the Beth Israel Hospital in a critical condition.\* For the preceding three weeks he had suffered from severe headaches and soreness of the mouth. Roentgen-rays of the teeth had revealed two "infected teeth" which were removed two weeks before entry. Since that time he had taken numerous tablets of anacin † and lullit † and had in one day ingested a total

\* We wish to thank Drs. Harry Linenthal and William Dameshek for permission to use the clinical and laboratory data, and Dr. Bernard Goldberg for many helpful suggestions and criticisms.

† Both anacin and lullit contain acetphenetidin, acetylsalicylic acid and caffeine.

TABLE I

Date	Hb. (Sahl) 13.8 gm. = 100%	Red Count	White Count	Per Cent									
				Neutro- philes	Baso- philes	Eosino- philes	Myelo- cytes	Myelo- blasts	Metamye- locytes	Large Lympho- cytes	Small Lympho- cytes	Mono- cytes	
2- 6-34	90	5,470,000	1000* 1500 2200	52	1	3					15	27	2
2- 8-34	85	5,705,000	1250* 2250	43	4	4					9	39	1
2-28-34	95	6,330,000	2550	53	4	1	1				5	33	3
3-15-34	97	5,955,000	2200* 2650	60	3	2					12	18	5
4-22-34	85**	5,500,000	2600	62	1	2					9	20	5
5-12-34	85**	6,100,000	1875	58	2	4					10	21	3
1-25-38	85	5,610,000	875	46	2	4	2	2			7	37	
8- 3-38	86	4,385,000	800* 1200	45	3				1		13	36	1

\* Different pipettes.

\*\* Tallqvist.



of 35 grains of acetphenetidin. Mouth washes had also been prescribed. The headaches became worse, the mouth more sore. About one week before entry "pus" formed about his gums. At this time, because of the severe headaches and progressive weakness, the patient went to bed. Six days before entry, twitchings of the hands and legs were constantly present. Three days before entry he told his family that something "had burst inside of his head," following which the headache disappeared entirely.

Physical examination revealed a well developed and obese male, mildly confused. Both ear-drums were markedly injected. The conjunctivae were injected and there was a slight icteric tint to the sclerae. The gums were soft, red and spongy. Pressure at the gum margins caused exudations of pus. The tongue was heavily coated. A thick, white, tenacious membrane covered the hard palate and portions of the gums. The pharynx was moderately injected. There was a mild cervical adenopathy. The lungs revealed dullness and diminished breathing, tactile and vocal fremitus at the right base. Over the latter area and in both axillae many medium moist râles were heard. The heart was negative. The pulse was 120, the temperature 104° F., and the blood pressure 140 systolic and 78 diastolic. Blood examinations and other laboratory data are shown in chart 2. On August 29 the patient was quite toxic, and the mouth showed many ulcerations and a foul purulent discharge.

Treatment consisted of adenosine sulphate, 2 grams in 125 c.c. of saline, on the night of admission, and on the following day 1.4 grams in 150 c.c. of saline, a transfusion of 500 c.c. of blood, and an intravenous infusion of 1000 c.c. of saline and glucose 2½ per cent.

The dullness at both bases increased with the appearance of moist bubbling râles. The patient's condition became worse; the temperature remained elevated, ranging from 104 to 105.5° F.; the pulse rate fluctuated from 90 to 125; and the respirations rose from 30 to 50. He became incontinent of both urine and feces, semicomatose, and died on August 31. Permission for a postmortem examination was not obtained.

### DISCUSSION

The patient presented a marked leukopenia on each blood examination during 1934 and 1938. The various white cell elements were quantitatively but not qualitatively or relatively affected. Jackson and Parker<sup>3</sup> state that the majority of patients with leukopenia have some well recognized fundamental disorder to account for this, and that in some instances the leukopenia is unrelated primarily to the hematopoietic system. No etiology could be found for the leukopenia, and though this was at times fairly marked the patient enjoyed very good health for four and a half years. One can only conjecture as to the white cell count from 1934 to 1938. At no time was there any evidence of a significant lymphadenopathy. Splenomegaly was not found on repeated physical examinations, and the roentgen-ray conclusions in regard to this were inconclusive.

Individuals may exhibit a chronic leukopenia with few and vague symptoms.<sup>12</sup> The white cells may remain well below 4000 or show periodic fluctuations varying from normal to a severe leukopenia. In some, white cell counts of 2500 to 5000 occur with no symptoms, and the response to any infection is prompt and adequate, both quantitatively and qualitatively. In others, demands over and above that physiologically required cause a more severe leukopenia and not a leukocytosis. The bone marrow, with its low reserve of myelocytes, cannot respond, and a minor infection may lower still further the patient's resistance.<sup>12</sup> The white cell count of our patient was usually lower than 2000 cells, and probably belongs to the latter group of patients with chronic leukopenia.

TABLE II

Date	Hb. (Sahli)	Red Count	White Count	Smear	Other Data
8-28-38	80	3,490,000	350	24 cels counted. Polynuclear neutrophils 3. Lymphocytes 16. Polymorphonuclear leukocytes toxic with variation in size and shape and staining of granules. Lymphocytes vacuolated and atypical. No small lymphocytes seen. Metamyelocytes 2. Unclassified 3	
8-29-38	* 74 (11.5 gm.)	3,670,000	1350 a.m. 700 p.m.	11 cels seen: 1 polynuclear neutrophilic and 10 lymphocytes	Platelets 264,240. Reticulocytes 0.5%. CO <sub>2</sub> combining power 56.7%. Stool examination negative. N.P.N. 42 mg. Icteric index 10. Blood sugar 221 mg. Calcium 8.6 mg.
8-30-38	76	4,380,000	700 a.m. 500 p.m. 300 p.m.		Throat culture negative for hemolytic streptococci. Urine examinations show v.s.t. of albumin, 6-8 white cells per high power field and 2-4 fine granular casts

\* Evelyn Colorimeter.

In view of the persistent and marked leukopenia other blood disturbances must be considered. The absence of splenomegaly, of gastrointestinal bleeding, and of an anemia (except for the anemia prior to death) over a period of four and a half years are against Banti's disease. Though platelet counts were not done prior to the fatal illness they did not appear diminished from the examination of the blood smears. The patient's age and the absence of symptoms and physical findings, of abnormal or disproportionate increase in abnormal lymphocyte cells, and of an anemia rule against a diagnosis of aleukemic leukemia. The absence of anemia and bleeding, of a history of exposure to roentgen-ray or radium or the administration of benzol or arsenic derivatives eliminates the possibility of an aplastic anemia.

The patient himself had been questioned as to any drug ingestion at the time of each blood examination, and as far as can be determined had taken aspirin tablets only for his headaches and pains in the left knee. He had been advised by friends to take potassium iodide for his arthritis. The amytal medication, which had been prescribed after the first blood examination had revealed a leukopenia, did not affect the blood picture, since it has been shown that the barbituric acid derivatives do not produce agranulocytic angina.<sup>2</sup> If the history as obtained from the relatives can be considered accurate the symptoms of his fatal illness had already started even before any drugs containing acetphenetidin had been taken. Of more than 379 cases of agranulocytic angina reported up to the year 1938, Kracke<sup>13</sup> noted only three as possibly related to the ingestion of acetphenetidin and concluded that the evidence is not as yet adequate that phenacetin is capable of producing agranulocytosis.

It is of interest that the white cell count in January 1938 was 875, with 46 per cent neutrophiles, and on August 3, 1938, a few days prior to the onset of his final illness, 800 and 1200, with 45 per cent neutrophiles. The red cell count obtained at the later date showed a distinct drop from that of January, a fall from 5,610,000 to 4,385,000 cells. The hemoglobin value remained about the same, i.e., 86 per cent. Four days after the blood examination, on August 7, the patient's fatal illness began, with symptoms of headache and sore gums. On August 14, one week after the onset, two teeth were extracted. As has been pointed out by others,<sup>13</sup> a history of the extraction of teeth has been obtained in some patients and is of considerable significance in the etiology of agranulocytic angina. Though in our patient the fatal illness had already started before this, it was observed that his condition became much worse following the extraction. It was at this time that the patient was then given fairly large doses of drugs containing acetphenetidin. Following his admission to the hospital the white cell count was found to be 350 and few granular cells were seen on the smear. The red cell count had fallen further, to 3,490,000 cells. The patient presented a typical picture of agranulocytic angina. The blood transfusion resulted in an increase of the red cell count to 4,380,000. The white cell count rose to 1350 cells, possibly as the result of adenosine sulfate therapy, and showed but few granular cells on smear examination. As the patient's condition became worse the white cell count diminished and on the day of death fell to 300 cells.

We have been unable to find any report in the literature in which a persistent and practically asymptomatic leukopenia of unknown etiology and of this degree and duration was followed by the development of a typical and fatal agranulocytic angina. Minter<sup>14</sup> mentioned the case of a girl who had been

known to have a granulocytopenia of three years' duration, during which time the highest white cell count was 1700 and the highest percentage of polymorphonuclear leukocytes 32 per cent. At the end of this period agranulocytosis developed and the white cell count fell to 400, with 16 per cent polymorphonuclear leukocytes. The patient recovered with treatment, the white cell count rising to 4100, with 52 per cent polymorphonuclear leukocytes.

A depletion of available leukocytes in the blood-stream has been found even before the symptoms of agranulocytic angina start, and makes the organism more liable to severe infection. Severe infections may be an occasional cause of agranulocytosis but rarely give rise to the latter unless some underlying bone marrow dyscrasia is present.<sup>3</sup> The bone marrow has been considered a primary rather than a secondary factor in the production of agranulocytosis.<sup>12</sup> Jackson and Parker,<sup>3</sup> in reference to a report in the Journal of the American Medical Association on the importance of amidopyrine in the production of granulocytopenia, state that "the report does not say nor does it imply that all cases are due to the drug nor does it preclude the possibility that there may be some pre-existing bone marrow dyscrasia which affords a fulcrum upon which the drug may work." The latter half of this statement is strongly supported by the findings of a chronic and marked leukopenia in our patient. As to whether sepsis in our patient was the cause or the result of the agranulocytosis it is difficult to say. Either the course of the disease would have been the same regardless of whether acetphenetidin-containing drugs were taken or it may be said that the ingestion of these drugs hastened and intensified the severity of the illness.

### CONCLUSION

1. A case report is presented in which a chronic and asymptomatic leukopenia of four and a half years' duration and of unknown etiology terminated fatally in typical agranulocytic angina.
2. The onset of the fatal illness was independent of any drug ingestion.
3. The case presented strongly supports the theory that agranulocytic angina tends to occur in one in whom a bone marrow dyscrasia is already present, resulting in a diminution of the granular cells in the peripheral blood stream.

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## EDITORIAL

### ADVANCES IN CONTROL OF YELLOW FEVER

THE discovery by the American Commission in 1900 that yellow fever is caused by a filtrable virus and that it is conveyed by the bite of the mosquito, *Aedes aegypti*, largely determined the methods used to control this disease during the subsequent three decades. Yellow fever was known to persist in endemic form in a number of maritime centers in tropical America, but it was not known to exist outside of these foci in interepidemic periods. The successful eradication of the disease from Havana and Panama and later from other cities by rigid anti-aegypti control measures led naturally to the hope that by extending such measures to all known endemic foci the disease might be eradicated from this continent. No other vector of the disease had been discovered, and it was not known to attack any other animal. This hope was shared by the members of the International Health Division of the Rockefeller Foundation when they started the campaign against yellow fever more than ten years ago.

For a short time it appeared that their efforts had been nearly successful. However, occasional cases of yellow fever appeared in unexpected places which could not readily be explained. Finally, Soper et al. (1933)<sup>1</sup> reported an epidemic in rural areas of Espirito Santo, Brazil, a region in which *A. aegypti* does not exist. An intensive study was then begun by this group to determine the extent of this new epidemiological type of yellow fever. They relied mainly on two procedures. First, they attempted by means of a viscerotome to get a small specimen of liver tissue from every individual in the district who died of any acute illness of less than 10 days' duration. The changes in the liver in yellow fever are believed to be pathognomonic. Secondly, they examined the blood of large numbers of individuals for antibodies by the mouse protection test. Such antibodies appear in the plasma and apparently persist throughout life in patients who recover.

These studies showed that yellow fever was endemic in many widely scattered areas throughout the interior of Brazil and several adjacent South American countries in which it had not previously been recognized. The disease tends to appear as scattered cases or in small epidemics in areas in or adjacent to forests or uncleared land. Hence it was termed jungle yellow fever. The sparsity of human cases in some of these areas indicated that man can not be the primary reservoir of the infection. This must be sought in the wild animals of the jungle, probably in the monkeys. These are susceptible to infection experimentally, and in these regions from 20 to 25 per cent of the monkeys may show antibodies in their serum. Man does not constitute an essential part of this cycle, and is only incidentally affected.

<sup>1</sup> SOPER, F. L., et al: Yellow fever without *Aedes aegypti*. Study of a rural epidemic in the Valla do Chanaan, Espirito Santo, Brazil, Am. Jr. Hyg., 1933, xviii, 555.

A search for other vectors showed that many other species of mosquitoes and also certain ticks can convey the disease under experimental conditions. Individuals of three other species of mosquitoes, caught in the jungle, were found naturally infected with yellow fever virus.

The jungle yellow fever virus is identical with the ordinary virus in every respect except in the mode of its transmission. A man who acquires the disease in the jungle can infect *A. aegypti*, and be the starting point of an epidemic of the ordinary type. In both types of infection it is now known that a large majority of the cases of yellow fever are so mild that they are not recognized. After an epidemic as many as 70 per cent of the inhabitants of a locality may show antibodies in their blood, although few of them give a history of yellow fever.

These discoveries in no way lessen the importance of anti-aegypti measures, for this mosquito is still the most dangerous carrier as far as major urban epidemics are concerned. They do indicate the impossibility of eradicating the disease in this way, since effective anti-mosquito measures are impracticable in the jungle. An attempt to increase human resistance by vaccination appeared to be a more feasible procedure.

Shortly after the discovery by Stokes, Brown and Hudson that monkeys can be infected with yellow fever, Hindle (1928)<sup>2</sup> prepared a vaccine by treating the liver of infected monkeys with formol or phenol. Monkeys could be immunized with this material, but it was later shown that either the monkeys suffered an attack of yellow fever (from which they usually recovered), or the material was entirely inert.

The fact that only a living virus is effective as a vaccine against yellow fever introduces into the procedure a number of dangers which must be guarded against. The vaccine might cause an attack of yellow fever, or of encephalitis if a neurotropic strain is employed. If an attenuated virus is used, it might unexpectedly recover its original virulence. Also, the virus might get into the blood, and by infecting *A. aegypti* mosquitoes start an epidemic of the disease. The principal measures relied on to avoid these dangers are attenuation of the virus by various methods, the administration of immune serum with the vaccine, or both.

In 1931 Sawyer, Kitchen and Lloyd<sup>3</sup> first used suspensions of infected mouse brain (Theiler's neurotropic virus) and human immune serum in vaccinating 56 individuals in New York, with satisfactory results. This method was also employed successfully by Findlay<sup>4</sup> in London, who by 1938 had vaccinated 5,700 Europeans who were going to infected areas in Africa. No case of yellow fever is known to have occurred among them, although about 40 cases were reported from non-immunized Europeans in the same districts.

<sup>2</sup> HINDLE, E.: A yellow fever vaccine, Brit. Med. Jr., 1928, i, 976.

<sup>3</sup> SAWYER, W. A., KITCHEN, S. F., and LLOYD, W.: Vaccination against yellow fever with immune serum and virus fixed for mice, Jr. Exper. Med., 1932, lv, 945.

<sup>4</sup> FINDLAY, G. M.: Immunization against yellow fever, Trans. Roy. Soc. Trop. Med. and Hyg., 1934, xxvii, 437.

Meanwhile Lloyd, Theiler and Ricci<sup>5</sup> showed that the virus can be grown in cultures containing mouse embryo tissue and that such virus lost its viscerotropic properties but showed no increase in its neurotropism. This was substituted for the suspension of infected mouse brain, and in 1938 Soper and Smith<sup>6</sup> reported the results obtained by the use of this vaccine combined with immune serum. Like Findlay, they obtained satisfactory results with human immune serum, in that reactions were usually mild and that 35 of 37 cases tested had been immunized. However, the difficulty in getting adequate amounts of human immune serum would preclude using this method on a large scale. When they employed immune animal sera, difficulties were encountered in that either reactions were severe or many individuals failed to develop immunity.

Because of these difficulties recent efforts have been concentrated on methods of vaccination not requiring the use of immune serum. In 1933 Sellards and Laigret<sup>7</sup> had reported using live neurotropic mouse brain virus in man. In the first six cases the results were satisfactory, but of seven later cases, severe reactions occurred in two. Laigret<sup>8</sup> then devised a method of progressively attenuating the vaccine, and administered three doses of increasing virulence to 3000 individuals in French West Africa. Of these a third had more or less marked reactions and two showed symptoms of encephalitis or myelitis. Findlay also tried the use of an attenuated virus in monkeys, but concluded it was dangerous to use it in man without serum.

More success, however, attended the efforts of the Rockefeller Foundation group. They found that after prolonged cultivation in chick embryo from which the brain and spinal cord had been removed, the virus lost all of its viscerotropic and most of its neurotropic properties. It still caused encephalitis on intracerebral injection into mice, although the incubation period was prolonged. It would no longer do this in monkeys. On ordinary injection into monkeys (without immune serum) it either caused no clinical evidences of illness or at most a slight febrile reaction, yet it regularly induced complete immunity to subsequent injection of highly virulent strains of virus. This was associated with the appearance of protective substances in the blood.

Based on these observations, vaccination experiments were undertaken on human volunteers in small carefully studied groups, first in New York (Theiler and Smith, 1937) and later in Brazil by the Coöperative Yellow Fever Service. A single dose of this chick embryo virus was given without serum. As highly satisfactory results were obtained in the preliminary

<sup>5</sup> LLOYD, W., THEILER, M., and RICCI, N. I.: Modification of the virulence of yellow fever virus by cultivation in tissues in vitro, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1936, xxix, 481.

<sup>6</sup> SOPER, F. L., and SMITH, H. H.: Yellow fever vaccination with cultivated virus and immune and hyperimmune serum, *Am. Jr. Trop. Med.*, 1938, xviii, 111.

<sup>7</sup> SELLARDS, A. W., and LAIGRET, J.: Vaccination de l'homme contre la fièvre jaune, *Compt. Rend. Acad. Sci.*, 1932, cxciv, 1609.

<sup>8</sup> LAIGRET, J.: La vaccination contre le fièvre jaune, *Bull. Soc. Path. Exot.*, 1933, xxvi, 806.



trials, it was applied on a wider scale, and in 1938 Smith, Penna and Paoliello<sup>9</sup> reported their results on 59,532 cases vaccinated during 1937. In October, 1938, Soper<sup>10</sup> reported that 800,000 persons had been vaccinated during the preceding nine months, with equally satisfactory results, at a cost of between eight and nine cents each.

The vaccine in most cases caused no appreciable reaction. In from 15 to 25 per cent of the cases there was headache, and less frequently slight fever, weakness and grip-like pains, coming usually on the sixth or seventh day. In about 1.5 per cent or less the reaction may be incapacitating for a day or two. No alarming reactions and no cases of encephalitis have been observed.

Virus in low concentration has been found in the blood in a minority of the cases when tested by intracerebral injections into mice. However, attempts by Whitman (1939) to infect *A. aegypti* and transmit the infection from such cases were not successful. Peltier et al. (1939) were also unable to do this in vaccinated cases in French West Africa. The risk of starting an *A. aegypti* borne epidemic from vaccinated persons would therefore seem to be practically negligible.

As judged by protection tests on sample groups, immunity developed in from 90 to 95 per cent of the cases. If cases which received inert vaccine are eliminated, the number protected rises to from 95 to 97 per cent. Immune bodies do not begin to appear until after eight or nine days and are regularly present by the twenty-first day. They have persisted in practically all cases tested for a year, but often in reduced concentration. The duration of the immunity has not been determined. Animal and human experiments indicate that protection is afforded as long as antibodies persist. How long this will be and whether protection will outlast demonstrable serum antibodies is not yet known. The practical value of vaccination from the epidemiological standpoint can be determined only after a much longer period of observation. That protection is substantial is indicated by the fact that since the vaccination of the laboratory personnel was instituted no case of yellow fever has occurred among them, whereas before this deaths were distressingly frequent—including Stokes, Noguchi, Young, Lewis, and Hayne. As carried out at present in expert hands the procedure promises to be comparable in safety and effectiveness to vaccination against smallpox. Universal vaccination in the vast areas involved will be a colossal task, yet it would not be an excessive price to pay for the control of this scourge if its effectiveness on a large scale is demonstrated.

P. C.

<sup>9</sup> SMITH, H. H., PENNA, H. A., and PAOLIELLO, A.: Yellow fever vaccination with cultured virus (17 D) without immune serum, *Am. Jr. Trop. Med.*, 1938, xviii, 437.

<sup>10</sup> SOPER, F. L.: Yellow fever: the present situation (October, 1938) with special reference to South America, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1938, xxvi, 297.

## REVIEWS

*Diseases of the Skin.* By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (Edin.), and RICHARD L. SUTTON, JR., A.M., M.D., L.R.C.P. (Edin.). 1549 pages; 26 × 18 cm. Tenth Edition. C. V. Mosby Company, St. Louis. 1939. Price, \$15.00.

The recently issued tenth edition of Sutton and Sutton's *Diseases of the Skin* includes some mention of all the more recent important contributions to dermatologic literature. The new volume is an excellent reference text. The print and the illustrations are very good.

While this book is admittedly one of the best textbooks on dermatology in the English language the reviewer is disappointed to find in this new edition many of the defects which have detracted from its value in the past.

The authors devote too much space to personal and unproved theories. This is especially true in the parts dealing with the treatment of acne and with carcinoma of the skin.

The use of the term eczema is still as confused as in earlier editions; eczema rubrum, sclerorum, squamosis and other forms of clinical eczema are described which have no real nosologic significance. Contact dermatitis is termed contact eczema in some places.

The authors state that their section dealing with syphilis is sketchy. In addition it may be stated that it is inadequate and that the treatment routines recommended are in many instances not in accord with modern standards.

In summary, this excellent volume is badly in need of further revision.

F. A. E.

*The Art of Anaesthesia.* By PALUEL J. FLAGG, M.D. 491 pages; 23.5 × 16 cm. Sixth Edition Revised. J. B. Lippincott Company, Philadelphia, 1939. Price, \$6.00.

This is a well illustrated volume, in which a survey of the subject is given in an elementary but practical manner.

The newer anaesthetic agents, such as cyclopropane, divinyl ether and avertin, are discussed, in addition to the newer local and intravenous ones. An adequate discussion is given of the problem of dental anaesthesia.

The value of helium and carbon dioxide and the technics for their use are discussed. Oxygen therapy is mentioned and stressed; however, detailed discussion is lacking.

A very satisfactory description is given of the indications for and methods of intratracheal anaesthesia and the apparatus used.

The book is comprehensive in its scope. There is no attempt made to discuss the theory and physiology of anaesthesia. It should be found to be of considerable practical value.

Discrepancies noted in references to various pages and in the index do not interfere with the basic value of the book.

G. H. Y.

*Clinical Toxicology.* By CLINTON H. THIENES, M.D., Ph.D. 309 pages; 20.5 × 14 cm. Lea and Febiger, Philadelphia, 1940. Price, \$3.50.

A modern, pleasantly bound textbook of toxicology that deals with common poisons in a brief and direct manner. Differential symptomatology and pathology of

similar compounds are well brought out. The section on anesthetics and their impurities is to the point. Treatment, symptoms, diagnosis, and chemical identification are helpfully outlined. Tabulation of section outlines might be more convenient and cross reference to page number instead of chapter number would be helpful. Recommendation of sedatives to control tetanus convulsions is not in line with Howell's newer findings, but the book on the whole is up to date. It includes the toxicology of sulfanilamide. Tests for common poisons are briefly given.

C. A.

*Peripheral Vascular Diseases: Diagnosis and Treatment.* By WILLIAM S. COLLENS, B.S., M.D., and NATHAN D. WILENSKY, M.D. 243 pages; 25 × 16 cm. Charles C. Thomas, Springfield, Illinois. 1939. Price, \$4.50.

This is a compact and rather comprehensive survey of the more common vascular disturbances. It should be valuable from the viewpoint of correlating diagnosis, management and treatment of these diseases.

The more usual types of vascular disturbances, such as arteriosclerosis, thromboangiitis obliterans and Raynaud's disease, are discussed in detail. Old methods of treatment, as well as the most recent, are described. Suggestions are given as to the management of these conditions, e.g., medically, from the supportive viewpoint and also physio-therapeutic.

The value of vascular, sympathetic and nerve surgery is reviewed.

Diagnostic signs and symptoms are described. In attempting to maintain a practical tone to the book, physiology is not stressed.

For a book attempting to be comprehensive in scope, an undue amount of space is given to one specific form of therapy, e.g., intermittent venous occlusion. This is particularly true when it is realized that this method, similar to other physio-therapeutic measures, is limited in scope and that the status of any one method has not been firmly established.

This book should be valuable as a guide to the individual in private practice.

G. H. Y.

## COLLEGE NEWS NOTES

### COMMITTEE ON NOMINATIONS—1940-41

In accordance with provisions of the Constitution, President James D. Bruce has announced the appointment of the following Committee on Nominations for the coming year:

David P. Barr, St. Louis, Mo., *Chairman*  
Reginald Fitz, Boston, Mass.  
Fred M. Smith, Iowa City, Iowa  
Charles F. Tenney, New York, N. Y.  
Ernest B. Bradley, Lexington, Ky.

Drs. Barr and Fitz are selected from the Board of Regents; Drs. Smith and Tenney from the Board of Governors; Dr. Bradley from the membership at large.

The duties of the Committee on Nominations are to nominate candidates for the elective offices, Board of Regents and Board of Governors. The selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members from the respective States, Provinces or districts which will be represented by the nominees, if elected. The list of nominees for President-Elect and for the First, Second and Third Vice Presidents shall be submitted to all the Masters and Fellows of the College at least one month before the annual meeting, and the election of all nominees shall be by the members of the College at its Annual Business Meeting. This does not preclude nominations made from the floor at the annual meeting itself.

### THE ELECTION OF THE AMERICAN COLLEGE OF PHYSICIANS TO MEMBERSHIP IN THE UNITED STATES PHARMACOPOEIAL CONVENTION

At the thirteenth decennial meeting of the United States Pharmacopoeial Convention, held at Washington, D. C., May 14 and 15, 1940, under the Presidency of Dr. Walter A. Bastedo, F.A.C.P., New York City, the American College of Physicians was elected a member of the Convention and its delegates, Dr. Torald Sollmann, F.A.C.P., Cleveland, Dr. Charles F. Tenney, F.A.C.P., New York City, and Dr. Edward D. Spalding, F.A.C.P., Detroit, were seated. Dr. Sollmann was elected Chairman of the College delegation and during the meeting was appointed to the Committee on Constitution and By-Laws of the Convention.

The Convention was reported to be one of the most harmonious, democratic and progressive of the Pharmacopoeial Conventions held to date. It made provision for adapting the Pharmacopoeia to the accelerated tempo of the present time. It also instructed the Trustees to appoint a committee to plan such further and more radical changes as may be advisable, and to report within two years to a special meeting of the Convention.

New Officers elected were:

President—Dr. C. W. Edmunds, Ann Arbor, Mich.  
First Vice President—H. A. B. Dunning, Baltimore, Md.  
Second Vice President—Dr. Cary Eggleston, New York, N. Y.  
Third Vice President—George Moulton, Peterborough, N. H.  
Fourth Vice President—Dr. H. C. Wood, Jr., Philadelphia, Pa.  
Fifth Vice President—Robert C. Wilson, Athens, Ga.  
Secretary—L. E. Warren, Chevy Chase, Md.  
Assistant Secretary—Frank Delgado, Washington, D. C.  
Treasurer—W. Paul Briggs, Washington, D. C.

Dr. Walter A. Bastedo, retiring President, became Vice Chairman of the Board of Trustees. Of the fifty-one members on the Committee on Revision, eighteen are from the medical profession, of whom the following are Fellows of the American College of Physicians:

Dr. Walter A. Bastedo, New York, N. Y.  
Dr. Charles L. Brown, Philadelphia, Pa.  
Dr. William B. Castle, Boston, Mass.  
Dr. Arthur C. DeGraff, New York, N. Y.  
Dr. George W. McCoy, Washington, D. C.  
Dr. Virgil E. Simpson, Louisville (Vice Chairman)  
Dr. Soma Weiss, Boston, Mass.

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#### GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following reprints by members of the College:

Dr. Oscar G. Costa-Mandry, F.A.C.P., San Juan, P. R.—1 reprint;  
Dr. Paul A. Draper, F.A.C.P., Colorado Springs, Colo.—1 reprint;  
Dr. Everett C. Fox, F.A.C.P., Dallas, Tex.—1 reprint;  
Dr. Lawrence E. Geeslin (Associate), Atlanta, Ga.—5 reprints;  
Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa.—bound volume of reprints;  
Dr. Clifford W. Mack, F.A.C.P., Livermore, Calif.—2 reprints;  
Dr. John H. Musser, F.A.C.P., New Orleans, La.—27 reprints;  
Dr. Louis B. Owens (Associate), Cincinnati, Ohio—1 reprint;  
Dr. Marjorie E. Reed, F.A.C.P., Plymouth, Pa.—2 reprints;  
Dr. Joseph Rosenfeld, F.A.C.P., Youngstown, Ohio—1 reprint;  
Dr. Merritt H. Stiles, F.A.C.P., Philadelphia, Pa.—2 reprints.

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Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, was appointed May 18, 1940, a member of the Committee on Advertisements and Commercial Exhibits of the American College of Physicians, filling the vacancy caused by the resignation of Dr. William D. Stroud, F.A.C.P. Dr. Stroud had served some years on this Committee and had made a real contribution, especially in connection with the new regulations governing the admission of commercial exhibits.

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At the annual meeting of the Austen Riggs Foundation, Inc., held in Stockbridge, Mass., on May 11, 1940, Dr. Horace K. Richardson, F.A.C.P., was elected Medical Director of the Foundation, succeeding Austen Fox Riggs, F.A.C.P., who died on March 5, 1940.

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Dr. Juan A. Pons, F.A.C.P., San Juan, P. R., has resigned as Assistant Professor of Medicine at the School of Tropical Medicine of Puerto Rico and is now engaged in private practice and head of the medical service of the Presbyterian Hospital, San Juan.

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Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "Nutrition and Deficiency Disease, with Special Reference to Vitamins" before the Cumber-

land County Medical Society at Portland, Maine, on April 25. He also presented a paper on "Factors Involved in Digestion and Absorption in Deficiency Disease" before the annual postgraduate lectures of the Attending Staff of Mercy Hospital, Philadelphia, May 13, 1940.

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Dr. August A. Werner, F.A.C.P., St. Louis, Mo., delivered two addresses under the auspices of the Postgraduate Committee of the Iowa State Medical Society at Marshalltown, Iowa, May 7, and at Ames, Iowa, May 8. The title of the addresses was "The Anterior Pituitary Gonad Relationship in the Female." Dr. Werner also addressed the Central District Medical Society, Davenport, Iowa, May 16, on the same subject.

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The Sixteenth Scientific Sessions of the American Heart Association were held in New York City, June 7-8, 1940, under the presidency of Dr. William D. Stroud, F.A.C.P., Philadelphia. Dr. William Goldring, F.A.C.P., New York, was chairman of the program committee. Twenty-eight papers appeared on the four sessions and twenty-three of the contributors were either Fellows or Associates of the American College of Physicians.

A cardiovascular exhibit was held under joint auspices of the American Heart Association and the American Medical Association. Among the exhibitors were the following:

- Radiology and Pathology of Heart Disease, Dr. Hugo Roesler, F.A.C.P., Philadelphia;  
The Effect of Tobacco Smoke and Nicotine Upon the Normal Heart and Upon the Heart with Myocardial Infarction: An Experimental Study on Dogs, Dr. Samuel Bellet (Associate), Philadelphia;  
Salient Public Health Features of Rheumatic Heart Disease, Dr. O. F. Hedley, F.A.C.P., Philadelphia;  
The Fluoroscopic Diagnosis of Cardiac Infarction Following Coronary Artery Occlusion, Dr. Arthur M. Master, F.A.C.P., Dr. Richard Gubner and Arthur Grishman, New York;  
Venous Pressure Studies in Cardiovascular and Peripheral Vascular Diseases, Dr. J. Ross Veal and Dr. Hugh Hussey (Associate), Washington, D. C.;  
Cardiovascular Disease in Advanced Years, Dr. Louis B. Laplace, F.A.C.P., Philadelphia;  
Experimental Endocarditis Induced by Intravenous Inoculation of *Streptococcus Viridans*, Dr. W. J. MacNeal, F.A.C.P., Dr. Martha Spence and Dr. Marie Wasseen, New York;  
(A) Lymphedema. (B) Deproteinized Pancreatic Extract in the Treatment of Intermittent Claudication, Dr. A. Wilbur Duryee, F.A.C.P., and Dr. Gerald H. Pratt, New York;  
Diagnostic Procedures in Peripheral Arterial Disease, Dr. Hugh Montgomery (Associate), Dr. Meyer C. Naide and Dr. Norman E. Freeman, Philadelphia;  
Plethysmographic Method for the Study of Blood Flow and Vascular Responses in the Extremities, Dr. David I. Abramson, F.A.C.P., and Dr. Fanny Senior, Cincinnati;  
Classification of "Essential" Hypertension, Dr. Henry A. Schroeder (Associate), New York;  
Cine-roentgenographic Studies of the Human Pulmonary Circulation, Heart Chambers and Greater Blood Vessels (Robb and Steinberg Method), Dr. William H. Stewart, F.A.C.P., and Dr. Charles W. Breimer, New York.

Under the sponsorship of the Florida Medical Association, in coöperation with the Florida State Board of Health, the eighth annual graduate short course for doctors of medicine was offered at Jacksonville, June 24-29. On a six-day program, five hours were given to Pediatrics, five hours to Gynecology, six hours to Obstetrics, four hours to Venereal Diseases, six hours to Surgery, three hours to Orthopedic Surgery and six hours to Medicine. In addition, there was a special dinner and round table for Surgery and one for Medicine. Dr. Henry M. Thomas, F.A.C.P., Associate in Medicine, Johns Hopkins University School of Medicine, presented the courses in Medicine and conducted the medical round table. Dr. T. Z. Cason, F.A.C.P. and College Governor for Florida, Jacksonville, was chairman of the postgraduate committee. A shorter postgraduate program or graduate seminar of three days was also offered under the same auspices for Negro doctors of medicine.

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The forty-third annual meeting of the American Gastro-enterological Association was held at Atlantic City, June 10-11, 1940, under the Presidency of Dr. Irvin Abell, F.A.C.S., Louisville, Ky. Among Officers of the organization are Dr. Andrew C. Ivy, F.A.C.P., Chicago, First Vice-President; Dr. Russell S. Boles, F.A.C.P., Philadelphia, Second Vice-President; Dr. A. F. R. Andresen, F.A.C.P., Brooklyn, Secretary; Dr. A. H. Aaron, F.A.C.P., Buffalo, Treasurer; Dr. Sara M. Jordan, F.A.C.P., Boston, Recorder. Dr. Chester M. Jones, F.A.C.P., Boston, and Dr. Ernest H. Gaither, F.A.C.P., Baltimore, are members of the Council; Dr. Albert M. Snell, F.A.C.P., Rochester, Minn., and Dr. Walter L. Palmer, F.A.C.P., Chicago, are members of the Committee on Admissions and Ethics.

Twenty-six individual presentations, dealing with Gastro-enterological subjects, were made, sixteen of the contributors being either Fellows or Associates of the American College of Physicians. Examination of the membership list of the Society reveals that of thirty-three senior members, twenty-six are Masters, Fellows or Associates of the American College of Physicians; of the one hundred and sixteen active members, seventy are Fellows or Associates of the College; of eighteen associate members, eleven are Fellows of the College; or, of a total membership of one hundred sixty-seven, one hundred and seven (or 64 per cent) are members of the American College of Physicians.

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Emory University Alumni Clinic Week was held in the medical building of the School of Medicine, Atlanta, June 4-7. All white physicians, regardless of the medical school from which they graduated, were invited to attend, and there was no fee or charge made. The clinic week is held under the auspices of the physicians of the Fulton County Medical Society and Emory University. Clinics were conducted primarily by Atlanta physicians from Tuesday through Friday. Twenty Fellows or Associates of the College participated in the clinic program.

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Dr. Everett C. Fox, F.A.C.P., Dallas, Tex., was recently elected President of the Dallas Southern Clinical Society.

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Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn., addressed the 69th annual session of the California Medical Association, held in Coronado May 6-9, on "Endocrinology: A Critical Appraisal."

The Connecticut State Medical Society held its 148th annual meeting in Hartford, May 22, under the presidency of Dr. Joseph I. Linde, F.A.C.P., New Haven. Guest speakers on the general program included Dr. William S. McCann, F.A.C.P., Rochester, N. Y., and Dr. T. Grier Miller, F.A.C.P., Philadelphia, Pa.

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Dr. Paul D. White, F.A.C.P., Boston, Mass., was the guest speaker at a meeting of the Hezekiah Beardsley Pediatric Club.

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Among Fellows of the College who addressed the 149th annual meeting of the New Hampshire Medical Society, held in Manchester May 14-15, were:

Dr. Elliott P. Joslin, Boston, Mass.—“Diabetic Hazards and How to Meet Them”;  
Dr. Priscilla White, Boston, Mass.—“Diabetes in Children and Adolescents: Problems and Management; Pregnancy in the Diabetic”;  
Dr. Alexander Marble, Boston, Mass.—“Diet and Insulin”;  
Dr. Cornelius P. Rhoads, New York, N. Y.—“Vitamins”;  
Dr. Nathan B. Van Etten, New York, N. Y.—“The Education of the Intern.”  
Dr. Van Etten later addressed the society banquet on “An American Health Program.”

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The 53rd annual meeting of the North Dakota State Medical Association was held in Minot May 6-8, under the presidency of Dr. Harry A. Brandes, F.A.C.P., Bismarck. Dr. Charles N. Hensel, F.A.C.P., St. Paul, Minn., presented a symposium on essential hypertension and Dr. Paul A. O'Leary, F.A.C.P., Rochester, Minn., spoke on “The Eczemas.”

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The Ohio State Medical Association held its 94th annual meeting in Cincinnati May 14-16. Among the speakers at the general sessions of this meeting were:

Dr. William Osler Abbott (Associate), Philadelphia, Pa.—“The Rôle of Small Intestinal Intubation in the Treatment of Intestinal Obstruction and in the Diagnosis of Obstructing Lesions”;  
Dr. Raymond A. Ramsey (Associate), Columbus, Ohio—“Treatment of Disorders of the Thyroid”;  
Dr. Sidney E. Wolpaw (Associate), Cleveland, Ohio—“Diagnosis of Early Pulmonary Tuberculosis.”

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The Oklahoma State Medical Association held its 48th annual session in Tulsa May 6-8. Guest speakers at the general scientific sessions included Dr. Horton R. Casparis, F.A.C.P., Nashville, Tenn.—“Tuberculosis and the General Practitioner; Medical Aspects of Child Behavior,” and Dr. Alphonse McMahon, F.A.C.P., St. Louis, Mo.—“Effect of Aminophylline on the Electrocardiogram; Group Hospital Insurance.”

Dr. McMahon, Vice President of the American Medical Association, spoke at an evening general meeting on “The Medical Profession, Its Aims and Responsibilities.” During this meeting Dr. Henry H. Turner, F.A.C.P., Oklahoma City, was installed as president of the Association.

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Dr. Horton R. Casparis, F.A.C.P., Nashville, Tenn., spoke on “Recent Advances in Chemotherapy” and “Recent Attitudes Toward Thymic Conditions”; and Dr.



James G. Hughes (Associate), Memphis, Tenn., spoke on "The New Tuberculin Patch Test" at the annual meeting of the Oklahoma Pediatric Society, May 6, at Tulsa.

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Among the guest speakers on the scientific program of the general meetings of the 74th annual session of the Texas State Medical Association, held in Dallas, May 14-16, were:

- Dr. Frank J. Heck, F.A.C.P., Rochester, Minn.—"Iron Requirements in Childhood and Adult Life";  
 Dr. Alan Brown, F.A.C.P., Toronto, Ont.—"A Consideration of Some Common Pediatric Problems";  
 Dr. Arthur C. Christie, F.A.C.P., Washington, D. C.—"Diagnosis and Management of Cancer of the Breast."

Dr. William L. Powers (Associate), Wichita Falls, Dr. Walter G. Reddick, F.A.C.P., Dallas, and Dr. William S. Horn, F.A.C.P., Fort Worth, were among those who spoke at a symposium on sulfanilamide therapy. Among the speakers at the symposium on hematology were Dr. William Boyd Reading, F.A.C.P., Galveston, Dr. Alvis E. Greer, F.A.C.P., Houston, and Dr. Moise D. Levy, F.A.C.P., Houston.

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Under the presidency of Dr. James H. Hutton, F.A.C.P., Chicago, the Illinois State Medical Society held its 100th annual meeting in Peoria, May 21-23. Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, spoke on "Selection of Cases of Splenectomy," and Dr. Tom D. Spies, F.A.C.P., Cincinnati, Ohio, spoke on "Diagnosis and Treatment of Common Deficiency Diseases in the Adult."

The oration in medicine was delivered by Dr. Leonard G. Rowntree, F.A.C.P., Philadelphia, Pa. His subject was: "The Rôle of the Kidney in Cardiorenal-Vascular Disease."

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The University of Chicago announced that Dr. Anton J. Carlson, F.A.C.P., who is professor and Chairman of the department of physiology, Division of Biological Sciences, will become emeritus professor at the end of the current year.

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The following members of the College were among the speakers at the 81st annual session of the Kansas Medical Society held in Wichita, May 13-16:

- Dr. Arthur C. Curtis, F.A.C.P., Ann Arbor, Mich.—"Treatment of Edema";  
 Dr. Walter L. Palmer, F.A.C.P., Chicago, Ill.—"Treatment of Chronic Indigestion";  
 Dr. Soma Weiss, F.A.C.P., Boston, Mass.—"Cardiac Asthma and Pulmonary Edema";  
 Dr. Daniel V. Conwell, F.A.C.P., Halstead, Kan.—"A Clinical Approach to the Migraine Problem—Preventive Treatment";  
 Dr. Aaron A. Sprong (Associate), Sterling, Kan.—"Radiation of Leukemia."
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Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., spoke on "Treatment of Pneumococcal Pneumonia," and Dr. Thomas Parran, F.A.C.P., Washington, D. C., spoke on "The Public Health Aspects of Syphilis as It Concerns the General Practitioner" at the 159th annual meeting of the Massachusetts Medical Society in Boston, May 21-22.

At a symposium on sulfanilamide Dr. Conrad Wesselhoeft, F.A.C.P., Boston, spoke on "Management of Acute Streptococcal Infections of the Upper Respiratory Tract," and Dr. Chester S. Keefer, F.A.C.P., Boston, spoke on "Diagnosis and Treatment of Gonorrheal Arthritis."

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The New Mexico Medical Society held its annual session in Albuquerque, May 27-29. Among the Fellows of the College who spoke at this meeting were:

- Dr. Ray M. Balyeat, Oklahoma City, Okla.—"Diagnosis and Treatment of the Common Allergic Manifestations as Seen by the General Practitioner";  
Dr. Albert Soiland, Los Angeles, Calif.—"Further Notes on the Clinical Aspect of Ultra Short Wavelength X-Rays";  
Dr. Paul M. Bassel, Temple, Tex.—"Frequency of Spinal Cord Tumors and Their Diagnosis."
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Dr. William McCully James, F.A.C.P., College Governor for the Republic of Panama and the Canal Zone, delivered the first James Carroll Flippin Memorial Lecture at the 25th semiannual postgraduate clinic presented by the University of Virginia Medical Department at Charlottesville, April 5-6.

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At the recent annual meeting of the Federation of American Societies for Experimental Biology in New Orleans, La., Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., was elected president of the American Physiological Society, and Dr. Gustave P. Grabfield, F.A.C.P., Boston, Mass., was elected secretary of the American Society of Pharmacology and Experimental Therapeutics.

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The 174th annual meeting of the Medical Society of New Jersey was held at Atlantic City, June 4-6, 1940. Among the guest speakers were:

- Dr. Sydney R. Miller, F.A.C.P., Baltimore—"Chronic Nephritis and Its Treatment in the Light of Contemporary Renal Physiology";  
Dr. William D. Stroud, F.A.C.P., Philadelphia—"Gastrointestinal Disturbances in Cardiovascular Disease";  
Dr. Charles L. Brown, F.A.C.P., Philadelphia—"The Relation of the Anemias to Gastrointestinal Diseases";  
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia—"Factors Involved in Digestion and Absorption in Deficiency Disease";  
Dr. Charles C. Wolferth, F.A.C.P., Philadelphia—"Cardiovascular Symptomatology in Biliary Tract Drainage";  
Dr. Leonard G. Rowntree, F.A.C.P., Philadelphia—"Hyperinsulinism";  
Dr. William A. Swahn, F.A.C.P., Dr. Lester M. Morrison (Associate), and Dr. Chevalier L. Jackson, Philadelphia—"Gastritis. Diagnosis and Treatment";  
Dr. Samuel Bellet (Associate), Dr. Leon Schwartz (Associate), Dr. Alfred Kershbaum, and Dr. Richard H. Meade, Jr., Philadelphia—"The Effect of Tobacco Smoke and Nicotine Upon the Normal Heart and in the Presence of Myocardial Disease Produced by Coronary Artery Ligation: An Experimental Study in Dogs";  
Dr. Thomas Fitz-Hugh, Jr., Philadelphia—"Gastrointestinal Disturbances in the Hemorrhagic Blood Dyscrasias."

Scientific Exhibits were entered by:

- Dr. J. H. Clark, F.A.C.P., Dr. Albert Behrend, Dr. Helena E. Riggs, and Dr. Moses Behrend, Philadelphia—"Cerebral Complications Following Surgical Operations";
- Dr. J. Russell Twiss, F.A.C.P., New York—"Biliary Colic: Etiology, Diagnostic Significance and Treatment";
- Dr. William A. Swalm, F.A.C.P., Dr. Lester Morrison (Associate), and Dr. C. L. Jackson, Philadelphia—"Chronic Gastritis";
- Dr. Herbert T. Kelly, F.A.C.P., Dr. Edmund L. Housel, and Dr. William M. Emrey, Philadelphia—"Deficiency Disease";
- Dr. Louis L. Perkel, F.A.C.P., Jersey City—"Unusual Manifestations of Peptic Ulcer—Roentgen Demonstration."

There was a combined session on medicine and gastro-enterology, Dr. Thomas M. Kain, F.A.C.P., Camden, being chairman of the section on medicine and Dr. Hyman I. Goldstein (Associate), Camden, being chairman of the section on gastro-enterology. Dr. Clarence L. Andrews, F.A.C.P., Atlantic City, presented a paper on "Cardiovascular Disturbance in Gastrointestinal Diseases."

On the program of the combined session, pediatrics and radiology, Dr. William G. Bernhard (Associate), Newark, was one of the leaders in the discussion of diagnosis in connection with a symposium on "Blood Dyscrasias in Infancy and Childhood."

At the session on gastro-enterology, Dr. Manfred Kraemer, F.A.C.P., Newark, gave an address on "Common Diarrheas: Causes and Treatment"; Dr. Christopher C. Beling, F.A.C.P., Newark, gave a paper on "Gastrointestinal Disturbances in Neurological Disorders"; and Dr. D. Ward Scanlan, F.A.C.P., with Dr. Clarence Whims, both of Atlantic City, gave a paper on "Suppurative Cholangitis."

On the program of the section on medicine, Dr. John W. Gray, F.A.C.P., Newark, gave a paper on "The Management of Infected Tonsils, Teeth and Sinuses in Arthritis"; Dr. Thomas K. Lewis, F.A.C.P., Camden, gave a paper on "Résumé of Present-Day Treatment of Arthritis"; Dr. Ralph K. Hollinshed, F.A.C.P., Westville, a paper on "Coronary Artery Disease"; and Dr. Benjamin Saslow (Associate), Newark, a paper on "Complications of Diabetes."

Dr. Edward C. Rosenow (Associate), Rochester, Minn., addressed The California State Dental Association, May 14, on "The Prevention and Elimination of Infections In and About Teeth and Thereby of Systemic Disease."

Dr. Perry J. Melnick, F.A.C.P., Chicago, has been appointed pathologist to supervise a diagnostic service in connection with the establishment of a division of cancer control in the Illinois State Department of Health, in accordance with recently enacted laws. About \$18,000 has been appropriated. The work will be largely educational, emphasizing early diagnosis and early treatment.

Dr. David J. Davis, F.A.C.P., Dean of the University of Illinois College of Medicine, Chicago, has been appointed chairman of an advisory board to the division of cancer control.

In memory of the late Dr. Bernard M. Fantus, F.A.C.P., the new outpatient clinics of the Cook County (Ill.) Hospital group were dedicated on April 19. Dr. Fantus was formerly the Director of Therapeutics at the Hospital and the creator of the "blood bank" for quick transfusions.

Just preceding the meeting of the American Medical Association in New York City, June 10-14, The New York Post-Graduate Medical School offered several intensive courses; June 3-7, "Clinical Interpretations of Laboratory Data" by Dr. Maurice Bruger (Associate); June 3-8, "Diseases of the Liver and Biliary Tract" by Dr. Carl H. Greene, F.A.C.P., Dr. John Russell Twiss, F.A.C.P., and Dr. Rupert Franklin Carter. Following the American Medical Association meeting a ten-day symposium on medicine was conducted under Dr. Walter G. Lough, F.A.C.P.

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Dr. Thomas T. Mackie, F.A.C.P., New York City, addressed the American Proctologic Society at Richmond, Va., June 9-11, on "The Rôle of Avitaminosis in Rectal Bleeding."

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Among guest speakers on the program of the annual meetings of the National Tuberculosis Association, the American Trudeau Society and the National Conference of Tuberculosis Secretaries at Cleveland, June 3-6, were:

- Dr. Maxim Pollak, F.A.C.P., Peoria, Ill.—"Tuberculosis in Mental Institutions";  
Dr. William H. Weidman (Associate), Norwich, Conn.—"The Application of Laminagraphy in Chest Conditions";  
Drs. Richard M. McKean, F.A.C.P., George C. Thosteson, F.A.C.P., and Nathan Brooks, Detroit—"Treatment of Tuberculosis and Diabetes, A Ten Year Experience."
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Dr. Edward A. Strecker, F.A.C.P., Philadelphia, addressed a public meeting at Cincinnati, May 20, held in coöperation with the Cincinnati Academy of Medicine, Cincinnati Medical Hygiene Council and the Public Health Federation, his subject being "Alcoholism—A Personal and Social Problem." Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., presided.

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The American Rheumatism Association held its annual meeting at New York City, June 10, under the presidency of Dr. Philip S. Hench, F.A.C.P., Rochester, Minn. Dr. Hench's presidential address was entitled, "Acute Multiple Recurring Arthritis and Periartthritis: Forty Cases of a New Articular Disease."

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Dr. Julius L. Wilson, F.A.C.P., associate professor of medicine, Tulane University of Louisiana School of Medicine, New Orleans, was one of the lecturers in a series of postgraduate lectures in internal medicine, held at Montgomery, Ala., over a period of six weeks from April 26, for the benefit of physicians in nearby counties. The same lectures are to be repeated in other sections of Alabama.

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Dr. Francis G. Blake, F.A.C.P., Sterling professor of medicine at Yale University School of Medicine, New Haven, has been appointed acting dean. Dr. Blake is a graduate of Harvard University School of Medicine, 1913, and served on the staff of Peter Bent Brigham Hospital until 1916, when he joined the Rockefeller Institute for Medical Research for a year. In 1917 he became associate professor of medicine

at the University of Minnesota Medical School and two years later became associate in medicine at Rockefeller Hospital. From 1920-21 he was associate member of the Rockefeller Institute and from 1924-35 he was a member of its scientific board of directors. In 1921 he became the John Slade Ely professor of medicine at Yale University and served until 1927 when he became Sterling professor of medicine. Dr. Blake has served as president of the American Society for Clinical Investigation and American Association of Immunologists. He was chairman of the division of medical sciences of the National Research Council from 1933-36 and chairman of the Section on the Practice of Medicine of the American Medical Association in 1938. He has been a Fellow of the American College of Physicians since 1930 and has served on its Board of Governors and on its Board of Regents.

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Dr. Allen H. Bunce, F.A.C.P., Atlanta, has been made president-elect of the Medical Association of Georgia.

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Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, Washington, D. C., gave the fourteenth William Thompson Sedgwick Memorial Lecture of the Massachusetts Institute of Technology, April 11, on "Nutrition and the Nation's Health."

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It was recently announced that Dr. Charles E. Stewart, F.A.C.P., director of the Battle Creek Sanitarium, Battle Creek, Mich., will retire at the end of the present year. He has been connected with this institution since 1895.

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Dr. Frank J. Heck, F.A.C.P., Rochester, Minn., has been elected a vice president of the Minnesota State Medical Association.

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Dr. James M. Flynn, F.A.C.P., Rochester, N. Y., was recently elected president of the Medical Society of the State of New York. Dr. Peter Irving, F.A.C.P., New York City, was reelected secretary. This society will hold its 1941 meeting in Buffalo.

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Dr. George Morris Piersol, F.A.C.P., Philadelphia, addressed the New York Academy of Medicine, May 2, on the general problem of aging.

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Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, College Governor for Wisconsin, addressed the Columbus (Ohio) Academy of Medicine recently on "Endocrine Therapy in General Practice."

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Dr. Louis Hamman, F.A.C.P., Baltimore, has been elected president of the Association of American Physicians. Other officers included Dr. James H. Means, F.A.C.P., Boston, vice president, Dr. Hugh J. Morgan, F.A.C.P., Nashville, Tenn., secretary, and Dr. William S. McCann, F.A.C.P., Rochester, N.Y., treasurer.

## OBITUARIES

## DR. BERNARD FANTUS

Dr. Bernard Fantus died at his home in Oak Park, Illinois, on April 14, 1940, of hypertensive heart disease in his sixty-sixth year. He had been a Fellow of the American College of Physicians since 1919.

Dr. Fantus was born in Budapest, September 1, 1874. He attended the Real-Gymnasium in Vienna, came to America, continued his studies at the University of Illinois College of Medicine and received his M.D. degree in 1899. From 1902 to 1913 he was in charge of the Medical Dispensary at his alma mater. In 1908 he continued his postgraduate work at the University of Strasbourg and again in 1909 at the University of Berlin. He received a degree of Master of Science at the University of Michigan in 1917.

He was made Professor of Pharmacology and Therapeutics at the University of Illinois College of Medicine in 1903, which position he held until his death except for a period from 1924 to 1932 when he was Associate Professor of Medicine at Rush Medical College, teaching the clinical therapeutic courses which had previously been conducted by the well known Walter S. Haines.

Dr. Fantus' primary interest was in therapeutics. During the forty years of his practice he was the liaison officer between druggist and physician. The problems of coöperation between the two were laid at his door and received intelligent consideration. Druggists everywhere have remarked of late that "Pharmacy has lost its best friend in the medical profession." It was the intimate details of prescription writing and compounding which early received his attention. One is therefore not surprised that he was elected as a member of the Revision Committee of the United States Pharmacopoeia National Formulae and Recipe Book, nor that he was at all times actively participating in the affairs of the American Pharmaceutical Association. His books included works on prescription writing, candy medication, useful cathartics and the technic of medication. More recently he had been hard at work on *The Therapy of the Cook County Hospital* published from time to time in the *Journal of the American Medical Association*. His interest in the technic and art of medical therapeutics stimulated him to develop the Solutions Laboratory of the Cook County Hospital where he was director of Therapeutics. Special study was given to the reactions following intravenous administration of fluids. The exceedingly careful preparation of containers, solutions and tubing has resulted in almost complete absence of such reactions.

For twenty-two years Dr. Fantus acted as Editor of the *Year Book of General Therapeutics*, completing the 1939 edition just previous to his death. He was also editor of *Merck's Manual* and for twenty years edited the *Digest of Therapeutics*.

Dr. Fantus was the originator of the plan to form a convalescent park in the space between the Cook County Hospital, The Presbyterian Hospital, the Student YMCA and Rush Medical College. Through continued effort this large area has been cleared and planted. The new clinic building of the Cook County Hospital has been named in his honor.

From the layman's view the chief contribution of Dr. Fantus was in the establishment of the blood bank on March 15, 1937. This has been of inestimable value in an institution where the turn over is rapid and emergencies constantly at hand. No one acquainted with the situations constantly arising in large general hospitals doubts its value.

Dr. Fantus was a stimulating teacher. He inspired many younger men to investigate problems of therapeutics. He was interested in the health of the community. One of his last appearances was before a meeting of the Chicago Medical Society at which time he urged the society to broadcast the picture of acute appendicitis that the public might better appreciate the onset and symptoms of appendicitis, and the serious effects of delay and catharsis. He counseled the officers to spread the news by public education as has been done elsewhere.

He was a member of Phi Rho Sigma and Alpha Omega Alpha, of the Chicago Society of Internal Medicine as well as the American Medical Association, and the American Pharmaceutical Society. In 1933 he received the first honorary degree from the American Therapeutic Association for his work on more palatable mixtures of cod liver oil and castor oil.

Dr. Fantus is survived by his widow, his daughter and two brothers.

An inspiring teacher and practitioner who acquainted himself with the great details of the everyday problems of therapeutics has gone to his rest.

LEROY H. SLOAN, M.D., F.A.C.P.,

Governor of Northern Illinois

## DR. EDWIN BOSWORTH MCCREADY

Dr. Edwin Bosworth McCready, F.A.C.P., Pittsburgh, Pa., died November 3, 1939. He had been a Fellow of the College from 1917, and was Governor for western Pennsylvania for many years. During this term he was keenly active in plans for the future of the organization, and his counsel was most helpful.

Dr. McCready was born in Pittsburgh, the son of the late Robert J. McCready, M.D., and Delphine Bosworth McCready. His College training was received at Lafayette College, Easton, Pa., and the University of the South at Sewanee, Tenn. His medical training was received at Jefferson Medical College of Philadelphia, and the Medico-Chirurgical College of Philadelphia from which he graduated in 1903. He was a member of the Allegheny County Medical Society, Pennsylvania State Medical Society, the

American Medical Association and a past President of the American Therapeutic Society. For many years he was Director of the Mental Health Division of the Juvenile Court of Allegheny County, and Examining Psychiatrist at the Mayview Hospital and the Thorn Hill School for Boys.

Dr. McCready's work and papers on speech defects and variation from the normal mental and endocrine states are outstanding in these fields. He demonstrated by his work the superiority of medical psychologists over lay psychologists.

He was a member of the Calvary Episcopal Church, and is survived by his wife, Jessie Kyle McCready, and a daughter, Delphine Bosworth McCready.

CLEMENT R. JONES, M.D., F.A.C.P.,  
Pittsburgh, Pennsylvania

### DR. WALTER H. MACCRACKEN

Dr. Walter H. MacCracken, Dean Emeritus of the College of Medicine of Wayne University, passed away on March 3, 1940, after an illness of only two days.

Dr. MacCracken was born in Albion, New York, in 1870. He attended the old Benton Harbor College, where he received his A.B. degree. He received his M.D. degree from the University of Louisville. After internship, he practiced medicine for several years in Bowling Green, Kentucky, but in 1906 returned to the University of Louisville as an instructor.

In 1914 he accepted a professorship in the Detroit College of Medicine and became Dean in 1917. He held the position until 1935, when, because of an untimely illness, he resigned the deanship. During the period of his administration, Dr. MacCracken successfully guided the school through many difficulties. By his leadership the school maintained a Class A ranking among the medical schools of the United States and Canada—this during a period when many schools were discontinued because of low standards. This accomplishment is particularly noteworthy in view of the fact that as the Detroit College of Medicine and Surgery the school was an independent organization not a part of a university. Dr. MacCracken and his associates, however, recognized that the medical school should be a department of a university, and he was gratified when the Board of Education, after an interval during which the school was operated as a unit of the public school system, established the Faculty of Medicine as the medical department of Wayne University. This evolution gives the school the distinction of being the only municipally owned and controlled medical school in the country. Dr. MacCracken was beloved by his students because of his subtle witticisms and his informal teaching methods. He had the kindly, humorous and philosophical outlook so characteristic of the medical man of the old school.



He was a Fellow of the American College of Physicians, a member of the Detroit Academy of Medicine, the Saturday Night Club, the Wayne County Medical Society, the Michigan State and American Medical Associations, the American Ornithologists Union, the Association of Audubon Societies, the Wilson Ornithological Society and the American Museum of Natural History.

Dr. MacCraken's vocation was the preparation of the youth to be of the greatest service to humanity by the training of honest, conscientious physicians. His hobby was Natural History, and his avocation, Ornithology.

On April 1, 1940, a memorial service was held by the Faculty at the Wayne University School of Medicine. A Resolution was adopted and it was resolved that his death be recorded in the proceedings of the Committees on Administration and the Faculty Council of the College of Medicine, with sentiments of highest regard for his memory and a deep sense of loss on the part of his faculty colleagues.

Dr. MacCraken is survived by his wife Hattie, and a daughter, Dr Frances MacCraken, an Assistant Professor in the School of Medicine.

WILLIAM J. STAPLETON, JR., M.D., F.A.C.P.,

Associate Dean, Wayne University College of  
Medicine, Detroit, Michigan

## RECENT ANNOUNCEMENTS

Dr. Torald Sollmann, F.A.C.P., Dean of Western Reserve University School of Medicine, has announced that fellowships and scholarships have been awarded from the Crile Research Scholarship Fund for work at Western Reserve University during the summer as follows:

From the first-year class: two awards for work in the Department of Biochemistry and three awards for work in the Department of Anatomy;

From the second-year class: one award for work in the Department of Hygiene and Bacteriology, one award for work in Pathology, two awards for work in Physiology, one award for work in Pharmacology and one award for work in Biochemistry;

From the third-year class: one award for work in the Department of Hygiene and Bacteriology, one award for work in Surgery and one award for work in Pathology.

From Western Reserve University also comes the announcement that the John and Mary R. Markle Foundation of New York has appropriated \$4,100 for the continuation of studies of the "cause and treatment of ventricular fibrillation." The studies have been in progress for a year in the School of Medicine under the direction of Dr. Carl J. Wiggers, F.A.C.P., Professor of Physiology.

President Winfred G. Leutner of Western Reserve University has also announced that the Commonwealth Fund of New York has made appropriations totaling \$17,900 for the use of Dr. Wiggers in a three-year program of studies of extracardiac factors of circulation.

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Mr. Eli Lilly, Indianapolis, has made a grant of \$3,600 for the establishment of a fellowship in protein chemistry, through the committee on the chemistry of proteins of the division of chemistry and chemical technology of the National Research Council.

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### COMPETITION FOR WELLCOME MEDAL ANNOUNCED

The Association of Military Surgeons of the United States announces the annual competition for the Wellcome Medal and prize of \$500, established by the late Sir Henry Wellcome for research on subjects helpful to the objects of the Association.

The topic chosen for this year is "Medical and Sanitary Care of the Civilian Population Necessitated by Attacks from Hostile Aircraft." Five copies of the essay must be in the office of the Association in Washington, D. C., by August 20. The medal will be awarded at the annual meeting in Cleveland, October 10-12.

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### 1940 GRADUATE FORTNIGHT OF THE NEW YORK ACADEMY OF MEDICINE

The 1940 Graduate Fortnight of the New York Academy of Medicine will be held from October 14 to October 25, 1940. The subject of this year's Fortnight is Infections. The purpose of the Fortnight is to make a complete study and authoritative presentation of a subject of outstanding importance in the practice of medicine and surgery.

The Fortnight will present a carefully integrated program which will include morning panel discussions, afternoon clinics and clinical demonstrations at many of

the hospitals of New York City, evening addresses and appropriate exhibits. The evening sessions at the Academy will be addressed by recognized authorities in their special fields, drawn from leading medical centers of the United States. The comprehensive exhibit will include books and roentgenograms; pathological and research material; and clinical and laboratory diagnostic and therapeutic methods. It is also planned to provide demonstrations of exhibits.

Dr. Mahlon Ashford, F.A.C.P., Executive Secretary of the New York Academy of Medicine, 2 East 103rd St., New York City, will gladly furnish programs upon request.

#### RADIOACTIVE STANDARDS \*

A series of radioactive standards are being prepared under the direction of the Committee on Standards of Radioactivity of the National Research Council. These standards will be deposited at the National Bureau of Standards in Washington, D. C., to be issued as working standards to investigators who may desire them.

The standards under preparation at present are:

(1) Radium Standards

- (a) 100 c.c. solutions sealed in 200 c.c. Pyrex flasks containing  $10^{-9}$  and  $10^{-11}$  grams of radium to be used as emanation standards either directly or by subdilution.
- (b) 5 c.c. solutions sealed in Pyrex ampoules containing 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, 10, 20, 50 and 100 micrograms of radium to be used as gamma ray standards. If desired, these may be obtained in sets of 13 with two each of the 0.2, 2, and 20 microgram standards.

(2) Thorium Standards

Sealed ampoules containing sublimed  $\text{ThCl}_4$ . These may be used in preparing standard thorium solutions.

Directions for use will be furnished with the standards.

(3) Standard Rock Samples

The following rocks, ground to pass 40-mesh screen and be retained on 100-mesh screen are available in 100 gram samples.

- Quartzite (Virginia)
- Triassic diabase (Virginia)
- Milford granite (Massachusetts)
- Chelmsford granite (Massachusetts)
- Gabbro-diorite (Massachusetts)
- Columbia River Basalt (Idaho)
- Berea sandstone (Ohio)
- Dunite (North Carolina)
- Carthage granite (Missouri)
- Carthage limestone (Missouri)
- Deccan Trap (India)
- Kimberlite (South Africa).

These samples of rock will be analyzed for radium and thorium content and are intended for use as working standards to check methods used in extraction of radon and thoron from rock samples. They may be used for direct fusion in the electric furnace or for carbonate fusion.

All of the above samples will be analyzed at a number of laboratories equipped to make such measurements and ultimately certificates will be issued by the National Bureau of Standards. This work is in progress but will require considerable time for

\* This work is being supported in part by a generous grant from the American Philosophical Society to the Massachusetts Institute of Technology.

its completion so that final figures are available only for a part of the samples at the present time.

Accurate knowledge of the radioactive content of the materials of the earth's crust is of primary importance in many phases of geology, geophysics and cosmology. Reliable radioactive standards are also essential in studies of radium and thorium poisoning and in biological and medical investigations using the technique of radioactive indicators, or internal artificial radioactivity therapy. For the latter purposes calibrated standard sources of  $\beta$ -rays will be made available.

It is hoped that the standards which have been prepared by the Committee will provide all workers in these fields with a common basis for comparison of measurements and also improve the accuracy of all measurements of this type. It is likely that they will have other applications and the Committee would appreciate hearing from interested persons who may desire similar standards for their work. The Committee is also glad to coöperate as far as possible in aiding investigators to use these standards to the best advantage and welcomes specific inquiries regarding their use. It is urged that any suggestions regarding other desirable radioactive standards, not at present available, be submitted promptly to the Committee. In particular, it will facilitate the work of the Committee if those laboratories and individuals that can make use of these standards advise the Committee of their probable requirements.

Communications may be addressed to the Chairman, Professor Robley D. Evans, Department of Physics, Massachusetts Institute of Technology, Cambridge, Massachusetts.

L. F. CURTISS,  
CLARK GOODMAN,  
ALOIS F. KOVARIK,  
S. C. LIND,  
C. S. PIGGOT,  
ROBLEY D. EVANS.

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Men engaged in research in medicine, public health, ecology, agriculture, forestry, botany or zoölogy, geography, and other fields, will welcome the announcement that BIOLOGICAL ABSTRACTS is undertaking a more complete abstracting and segregation of the current research literature in bioclimatology and biometeorology. The section *Bioclimatology-Biometeorology* will appear within the section *Ecology* in BIOLOGICAL ABSTRACTS, and will be under the editorship of Mr. Robert G. Stone of the Blue Hill Observatory, Harvard University.

# ABSTRACT

## MINUTES OF THE BOARD OF REGENTS

MEETING NO. 1, MARCH 31, 1940

The first meeting of the Board of Regents, held in connection with the Twenty-fourth Annual Session of the American College of Physicians, occurred March 31, 1940, at the Cleveland Public Auditorium, Cleveland, Ohio, presided over by President O. H. Perry Pepper with eighteen members of the Board present and with Mr. E. R. Loveland acting as Secretary.

Minutes of the preceding meeting and communications were read by the Secretary.

By resolution, a proposal by Dr. Henry H. Lissner, F.A.C.P., that Fellows on reaching the age of sixty-five instead of being placed on the inactive dues-waived list be given the privilege of subscribing \$50.00 for active life membership was referred to the Finance Committee for study and report.

By resolution, the Regents directed that the College donate to the medical profession of Madrid, Spain, through the American Union for Nationalist Spain, Volumes XII, XIII and XIV of the "Annals of Internal Medicine."

By resolution, the Editor was directed to publish in the "Annals of Internal Medicine" a summary of the program of the Eighth American Scientific Congress.

The Secretary-General reported the deaths of the following 15 Fellows and 4 Associates since the preceding meeting of the Board of Regents, which brought the total deaths, since the last Annual Session, to 1 Master, 47 Fellows, 15 Associates, or a grand total of 63.

### *Fellows:*

Boardman, Walter Whitney, San Francisco, Calif., February 11, 1940  
Browning, Charles Clifton, San Marino, Calif., September 28, 1939  
Clayton, John Conover, Freehold, N. J., November 25, 1939  
Cowie, David Murray, Ann Arbor, Mich., January 27, 1940  
Falconer, William George, Clearfield, Pa., January 3, 1940  
Falkowsky, Charles, Jr., Scranton, Pa., December 28, 1939  
Hall, Josiah Newhall, Denver, Colo., December 17, 1939  
MacCraken, Walter H., Detroit, Mich., March 3, 1940  
McCready, Edwin Bosworth, Pittsburgh, Pa., November 3, 1939  
Nelson, Albert William, Battle Creek, Mich., January 5, 1940  
Osborn, Samuel, Lansing, Mich., December 4, 1939  
Ray, Charles Andrew, Charleston, W. Va., January 21, 1940  
Riggs, Austen Fox, Stockbridge, Mass., March 6, 1940  
Stevens, Martin Luther, Asheville, N. C., January 20, 1940  
Van Cott, Joshua Marsden, Brooklyn, N. Y., February 8, 1940

### *Associates:*

Broadwater, Norman Irving, Oakland, Md., February 26, 1940  
Cobey, James Carpinter, Frostburg, Md., January 29, 1940  
Pumyea, P. Clinton, New York, N. Y., January 18, 1940  
Robinson, Frank Hurd, Jr., Hornell, N. Y., November 22, 1939

Dr. Piersol also reported the following additional Life Members since the last meeting of the Board, stating that at previous meetings since the last Annual Session, he had reported five (5) new Life Members, which makes a total for the year of eighteen (18) and a grand total in the College of 134. Of the grand total, twelve (12) are deceased, leaving a balance of 122.

Anthony Bassler, New York, N. Y.  
 Samuel A. Brown, New York, N. Y.  
 George B. Crow, Burlington, Iowa  
 Horace K. Richardson, Stockbridge, Mass.  
 Thomas F. Duhigg, New York, N. Y.  
 William S. Kerlin, Shreveport, La.  
 Charles Thomas Way, Cleveland, Ohio  
 Edward LeRoy Bortz, Philadelphia, Pa.  
 Frederick Lane Brown, New Brunswick, N. J.  
 Walter R. Steiner, Hartford, Conn.  
 Harry R. Ryan, Rutland, Vt.  
 Charles Henry Sprague, Boise, Idaho  
 Lodovico Mancusi-Ungaro, Newark, N. J.

On motion by Dr. Charles H. Cocke, seconded by Dr. James E. Paullin, and regularly carried, the report of the Secretary-General was accepted and filed.

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, reported for that Committee. The Committee had held meetings on February 25, 1940 and March 31, 1940, at which the following candidates were selected for recommendation for election.

On motion by Dr. James E. Paullin, seconded by Dr. Francis G. Blake and regularly carried, it was

RESOLVED, that the following list of 156 candidates for Fellowship shall be and herewith are elected.

(List of elections published in the April Issue of this journal.)

On motion by Dr. James E. Paullin, seconded by Dr. Charles H. Cocke and regularly carried, it was

RESOLVED, that the following list of 144 candidates for Associateship shall be and herewith are elected.

(List of elections published in the April Issue of this journal.)

On recommendation of the Committee on Credentials one Associate was dropped from the Roster because of failure to take up election within one year.

Dr. Sydney R. Miller, continuing his report for the Committee on Credentials, offered the following analysis on the candidates elected to Associateship five years previous, whose maximum five-year term now had terminated:

Advanced to Fellowship .....	127
Deceased .....	2
Resigned .....	4
Failed to qualify and therefore dropped .....	18
	<hr/>
	151 Total

Thereupon, Chairman Miller presented the names of 18 Associates who had failed to fulfill the requirements for advancement and upon resolution regularly adopted these Associates were discontinued on the Roster.

Chairman Miller, continuing his report, nominated Dr. James B. Herrick, F.A.C.P., Chicago, and Dr. William Gerry Morgan, F.A.C.P., Washington, for election to Mastership in consideration of their positions of eminence and their past services to the American College of Physicians. Both nominations were seconded and their elections to Mastership were unanimous.

Chairman Miller also reported that the booklet descriptive of the College and its requirements for membership had been revised and the revision would be presented for review by the Regents later in the week.

President Pepper presented for consideration the presentation of the President's gavel at the time of his induction into office rather than at the end of his term as President. The custom heretofore in the College had been to present the gavel to the retiring President at the end of his term. Dr. Piersol pointed out that the idea of presenting the gavel to the retiring officer is one that is well founded in many societies, the tradition being that it is presented to him by his associates and confreres as a token of their appreciation and as a permanent record of his distinction in office.

After general discussion, Dr. Piersol moved that the present custom be continued; it was seconded and regularly carried that there be no change in this procedure.

Dr. Walter W. Palmer, Chairman of the Committee on "Annals of Internal Medicine" had no report to present. Dr. Maurice C. Pincoffs, Editor of the "Annals," reported that a meeting of the Committee would be held during the week to discuss the question of whether the journal should be extended in size. The journal has been enlarged during the current year in an effort to take up the lag in publication of many articles already accepted. President Pepper mentioned the problem of publishing large reviews, such as the annual rheumatism review, suggesting that the Committee on the Annals should consider this problem from the standpoint of expense and also from the standpoint of the large amount of space occupied to the exclusion of other articles. The rheumatism review has proved extremely popular and valuable.

The Executive Secretary, Mr. Loveland, presented the recommendation of the Executive Offices and of the Editor's Office that the publishing contract for the journal with the Lancaster Press be renewed for another year, from July, 1940, to June, 1941. Both the financial arrangements and service had been highly satisfactory to the College, and the proposal for continuation of the contract was on the same basis as for the preceding year, with no increase or decrease in the basic rates.

On motion by Dr. Pincoffs, seconded by Dr. Charles H. Cocke, and regularly carried, it was

RESOLVED, that the publishing contract with the Lancaster Press for printing the "Annals of Internal Medicine" be renewed for Volume XIV, July, 1940, to June, 1941.

Dr. Hugh J. Morgan, Chairman of the Committee on Postgraduate Education, asked for the approval of the Board of Regents for the printing of an appropriate small certificate of attendance to be given to those members of the College who take the Postgraduate Courses. Dr. Morgan had prepared a sample of the certificate to carry the signature of the President and Secretary-General of the College. Dr. Morgan moved that such a certificate of attendance be authorized, and Dr. Charles H. Cocke seconded the motion.

In the discussion of the motion, it was brought out that this was purely a certificate of attendance and not a certification of the work done; that the certificate should be comparatively small, so that the expense would be slight, and that a record of each certificate should be recorded in the College office; that the certificate should not be of a character recommended for framing, because the College does not want to be in the position of the old proprietary schools, particularly the postgraduate schools; that the certificate should not be spread very broadly, or without any particular control or evidence of accomplishment; that the certificate should not be subject to abuse for advertising purposes. Dr. Morgan again pointed out that it would be purely a certificate of attendance, and that the Postgraduate Courses are very carefully planned and the College is in a position to attest to the excellence of the courses, but not to the degree of efficiency any particular student might attain from attending the course.

Due to the fact that at a later meeting of the Board of Regents the subject of segregating the work of directing the pre-meeting courses to a sub-committee of the Board of Governors from the regular Committee on Postgraduate Education would be considered, action was deferred on the matter of the certificate.

Dr. Roger I. Lee inquired if the motive behind the suggestion for a certificate

was to improve and dignify these Courses and make them more desirable, or if the motive was merely to give a man something that he could show.

Dr. Morgan replied that the motive was to give an incentive and stimulus to men in the College to take the courses, and that the recognition of their taking the courses would add dignity; also that it might encourage the men who are giving the courses to put them on an ever increasingly high plane.

Dr. Morgan, continuing the report of his Committee: "The College Committee on Postgraduate Education wishes to report on the meeting of the Advisory Council on Medical Education, February 10 at Chicago, where the College was represented by Dr. James H. Means and Dr. Hugh J. Morgan. The Advisory Council on Medical Education adopted the following resolutions:

"(1) Inasmuch as the internship is now universally regarded as a part of the basic preparation for the practice of medicine and to be fully satisfactory must be integrated with the medical course proper, the Advisory Council on Medical Education recommends that the Association of American Medical Colleges in coöperation with national medical and hospital organizations and the Federation of State Medical Boards and state licensing bodies, and after consultation with the Council on Medical Education and Hospitals of the American Medical Association, should formulate minimum educational standards for the internship and should prepare a list of hospitals in this country which meet these standards."

"Through the insistence of members of the College, the phrase 'after discussion with the Council on Medical Education and Hospitals of the American Medical Association' was inserted in the resolution and the resolution was passed.

"I personally was not sure that the Association of American Medical Colleges was wise in making any such survey, but it wanted to do so because it felt it could render service to its students. It did seem important that we recognize the work that has been going on for many years, that has been done by the Council on Medical Education and Hospitals of the American Medical Association. That point was recognized by the Committee as a whole and was incorporated in the resolution.

"Your Committee points out that Dr. Morris Fishbein in the current issue of the Journal of the American Medical Association, devoted to medical education, has vigorously attacked the action of the Association of American Medical Colleges in their decision to go into the matter of evaluating internships. The second resolution adopted by the Advisory Council on Medical Education was as follows:

"(2) Inasmuch as the internship is now universally regarded as a part of the basic preparation for the practice of medicine, the Advisory Council on Medical Education recommends to the Federation of State Medical Boards that an internship of not less than twelve months and of satisfactory educational content be required for admission to the state licensing board examinations in all states."

"This report is made simply as a matter of information to the Regents."

The Board of Regents took no action on the above part of Dr. Morgan's report, whereupon Dr. Morgan continued: "Your Committee also wishes to report to the Regents now on a meeting of the Joint Conference Committee of the American Board of Internal Medicine, the American College of Physicians and the Council on Medical Education and Hospitals of the American Medical Association, held in Chicago, February 4, as an organization meeting. The Committee agreed that (1) a coöperative plan is now in force among these three organizations; (2) in general, procedure already adopted by the Council on Medical Education and Hospitals would be continued in the evaluation of residencies and fellowships in Medicine; (3) the Conference Committee will assist in the formulation of standards that will express more accurately the requirements for graduate training in Medicine; (4) when feasible, members of the American Board of Internal Medicine, or of the Committee of the



American College of Physicians, will accompany the Council's examiners to some of the hospitals under consideration in order to participate in the inspection; (5) application blanks and inspection reports will be submitted to the American College of Physicians and the American Board as promptly as possible after the completion of the survey; and, finally, a joint approval of this material will be made either by correspondence or conference, and the result of the Committee's decision relative to it will be transmitted to the Council on Medical Education and Hospitals of the American Medical Association.

"The Committee on Postgraduate Education also wishes to report that five Postgraduate Courses have been given preceding the Annual Session. Course No. 1, 'General Medicine,' under Dr. Cyrus C. Sturgis at the University of Michigan Medical School, was attended by 18 Fellows and 15 Associates; total, 33; Course No. 2, 'Medicine in Industry,' under Dr. Frank J. Sladen at the Henry Ford Hospital, Detroit, was attended by 3 Fellows and 2 Associates and 2 candidates for membership, and 31 non-members (23 of these non-members were registered directly by Dr. Sladen); total, 38; Course No. 3, 'Allergy,' under Dr. Robert A. Cooke, at the Roosevelt Hospital, New York City, was attended by 2 Fellows and 6 Associates; total, 8. This course was limited to 8, and many applicants had to be turned away; Course No. 4, 'Postgraduate Survey of the Hematologic Diseases,' under Dr. Charles A. Doan at the Ohio State University College of Medicine, Columbus, was attended by 22 Fellows and 15 Associates, and 1 non-member; total, 38; Course No. 5, 'Cardiovascular Diseases,' under Dr. Fred M. Smith at the State University of Iowa College of Medicine, was attended by 16 Fellows and 11 Associates; total, 27. There was a grand total of 144 students, 110 of whom were members (61 Fellows and 49 Associates) of the College. They were drawn from 33 States and from Canada."

On motion by Dr. Morgan, seconded by Dr. William D. Stroud, and unanimously carried, it was

RESOLVED, that a letter of thanks, conveying sincere appreciation of the Board of Regents for the effort and time devoted to giving these Courses, be sent to each of the five Directors of the 1940 Postgraduate Courses of the College.

At this juncture, Dr. Morgan continued his report: "I want to bring before the Regents the following matters: (1) the desirability of passing on to the Board of Governors the continuation study program initiated by the College in 1938, which has been under the direction of the Regents' Committee since that time. The Courses have become established as a definite part of the College's educational program. I personally feel that since the Governors have expressed keen interest in this aspect of the College work and since they are in closer touch with members who attend these Courses probably the responsibility of arranging and organizing the Courses should be passed on to them. (2) The Conference Committee of the Council on Medical Education and Hospitals of the American Medical Association has come into being, and the College thus has an opportunity to participate in the definition of standards for medical internships, assistant residencies and residencies, to help in a survey of institutions for such residencies, and to guide the Council of the American Medical Association in its evaluation of these residencies. I should like to recommend that the Regents delegate the responsibility for the annual Postgraduate Courses and the Conference Committee work to a committee of the Governors. Both of these points are matters that ought to be gone into after due consideration, and I do not ask for any action. In fact, I think it might be well to defer action until a subsequent meeting of the Regents, after they have had adequate time to consider the matter."

President Pepper pointed out that the work of the Committee on Postgraduate Education of the College had proved a very arduous task, and that the Chairman has been called upon for tremendous amount of work and travel. Dr. Pepper expressed the hope that the Regents would continue to control the policy of the College in relation to graduate education, and that he thought it would be a mistake to take the entire

matter out of the Regents' hands, whereas it would be quite practical to delegate the direction of the Postgraduate Courses to a committee of the Governors and thus lessen the duties of the Regents' Committee.

Dr. Pepper also expressed the opinion that the pre-meeting Postgraduate Courses ought to be correlated in some way with the sectional or regional meetings, and that the Board of Governors should be asked to create a committee to take charge of these Courses, but that the Regents should continue their Committee, perhaps as one of educational policy, and that Dr. Morgan, if possible, should be persuaded to continue as Chairman.

Dr. Morgan then asked for the Regents' consideration of the establishment of a different kind of fellowship, namely, in addition to its Research Fellowships, it should establish fellowships in Clinical Medicine, to the end that a man who has had an internship, or an assistant residency, but who has failed to get a third or fourth year as resident may have an opportunity to continue his institutional work. There are not enough residencies to go around for the number of men who are asking for them, Dr. Morgan contended, and he felt that a modification of the College's present Research Fellowship, or, perhaps, an extension of it, to include clinical fellowships would be very gratefully received by many men who hope to qualify for the American Board of Internal Medicine certification and later for admission to the College.

In the general discussion that followed, Dr. Cocke pointed out that inasmuch as this would entail a large financial obligation on the part of the College, the Finance Committee would have to be consulted, and that action should be taken only after due consideration at a full meeting.

President Pepper pointed out that there were three points in the report of the Committee on Postgraduate Education which will come up for later discussion: (1) the giving of some form of certificate of attendance for those completing the Postgraduate Courses, this certificate to be in a simple form which would discourage its use in an undesirable way and would merely state that the College and the Credentials Committee had taken cognizance of the fact that the student had pursued the course; (2) the matter of delegating to the Board of Governors certain responsibilities for the conduct of the Postgraduate Courses; (3) the establishment of fellowships in Clinical Medicine.

On motion put and seconded and regularly carried, it was

RESOLVED, that the report of the Committee on Postgraduate Education be received and filed.

Due to the unavoidable absence of Dr. James Alex. Miller, Chairman, the report of the Committee on Finance was made by Dr. Roger I. Lee:

"The Finance Committee held a meeting this morning with the Treasurer and went over the College accounts, budgets and other data. The Committee is happy to report that the finances of the College are in excellent condition, with a surplus of income over expenditures for the current year. The Finance Committee recommends the transfer of \$25,000.00, or more, from the General Fund to the Endowment Fund, with the hope of building up the Endowment Fund to some substantial figure, so that it may produce an income which will be of great value to the College. The Finance Committee recommends that this be done in these so-called profitable years against the possibility of lean years. The Finance Committee would point out that the income from investments has continued at about 4 per cent, which it regards very favorable. There was a capital loss of about \$5,000.00 in securities sold, which, however, is somewhat counteracted by the fact that there has been an improvement in the market value of securities still held. One item that gave the Finance Committee concern was the fact that in 1936 the percentage of bonds was about 85 per cent of total holdings, but gradually there has been a reduction in the percentage of bonds, partly on account of the depreciation of some of these bonds and the appreciation of

stocks, so that now the percentage of bonds is under 50 per cent. The stocks that the College owns are mainly preferred stocks, and the percentage of common stocks is still very low, about 10 per cent, in general terms. It is the decision of the Finance Committee, unless otherwise directed by the Board of Regents, to develop the percentage of bonds, in order to restore that percentage to a considerably higher figure than at the present time."

On motion by Dr. George Morris Piersol, seconded by Dr. Walter W. Palmer, and unanimously carried, it was

RESOLVED, that \$25,000.00 shall be transferred from the General Fund to the Endowment Fund as of this date.

President Pepper pointed out that the Finance Committee had been following the advice all along of its investment counsellor, the Girard Trust Company.

Dr. Lee stated that the Finance Committee had not in the present instance voted to approve some of the suggestions of the investment counsellor, in regard to the purchase of more stocks, but had approved their recommendations for the purchase of bonds.

On motion by Dr. Robert A. Cooke, seconded by Dr. Charles H. Cocke, and unanimously carried, it was

RESOLVED, that the report of the Finance Committee be approved and filed.

On motion by Dr. James E. Paullin, seconded by Dr. Sydney R. Miller, and regularly carried, it was

RESOLVED, that an appropriation of \$134.38 be made to cover the traveling expenses of Drs. Hugh J. Morgan and James D. Bruce, College representatives on the Conference Committee on Postgraduate Training in the field of Internal Medicine, to the Chicago Conference, February 4 and February 11-13.

President Pepper then called for a report of the Committee on Survey and Future Policy.

In the absence of Dr. James Alex. Miller, Chairman, Dr. Maurice C. Pincoffs reported that the Committee had held a very brief meeting with three members present and with no report other than one of progress to make. Certain matters which had come up at the preceding meeting of the Committee at Philadelphia in December, 1939, were discussed. One of these was the use of educational films, or the possible rôle of the College in connection with educational films. The Chairman, Dr. James Alex. Miller, had contacted the Film Center of New York City and obtained certain sample films for showing at the end of the First General Session of the Cleveland meeting. The Film Center was reported to be a source of information as to what it might cost the College if it instead of mobilizing films now extant and loaning them out were to make films of its own for distribution to its regional meetings, or for such other educational purposes. The Film Center had estimated that a short film would cost from \$2,500.00 to \$3,500.00, and another organization reported that the cost would be \$3,000.00 and upward. The impression of the Committee on Future Policy and Survey was that such figures wouldn't compare well with university experience in making films, and that no program could be based on such figures without further investigation.

Dr. Pincoffs stated that there had been further discussion of the feasibility of publishing in the "Annals of Internal Medicine," from month to month, announcements that relate to available educational opportunities in Internal Medicine. The Committee felt that if such notices were restricted to those of universities and of comparable bodies, such as the New York Academy of Medicine, it would offer no great difficulty to the Executive Secretary's office and the Editor's office to publish these, and they might be of considerable utility to the members who are looking at certain times of the year for postgraduate courses. The Committee felt that it would be better policy not to include the more general meetings, which are not strictly in the field of Internal Medicine.

President Pepper referred to the fact that Dr. James Alex. Miller had contributed a chapter to the College History, and that said chapter was in the hands of Dr. Pincoffs and available for any of the Regents to read. In the latter part of the chapter, Dr. Miller had discussed the present plans and future hopes of the Survey Committee.

Continuing, Dr. Pepper said that the Committee on Scientific Exhibits had been for some reason instructed to report through the Committee on Future Policy and Survey, but asked the Chairman, Dr. Francis G. Blake, for any report he might have available.

Dr. Blake reported briefly of progress. The Committee had been collecting a certain amount of information concerning the holding of scientific exhibits, and another meeting of the Committee will soon be held, when more definite recommendations will be presented.

On motion by Dr. D. Sclater Lewis, seconded by Dr. Roger I. Lee, and regularly carried, the report of the Committee on Future Policy and Survey and Dr. Blake's report were received and filed.

(Many members of the Regents and Governors, as well as some members of the College viewed the films referred to, as shown in the public meeting room on Monday, April 1, and the general consensus of opinion was that this activity would not justify the necessary expenditures; in other words, that the College could utilize its funds in other directions to the greater advantage of its members.)

At the request of President Pepper, Mr. Loveland, as secretary, reported that the Historian, Dr. William Gerry Morgan, had sent a message to the effect that it had been impossible to have the College History published and presented at this time, due to several contributions not yet being completed. The Regents furthermore had instructed Dr. Morgan to cover the first twenty-five years in the College History, which would include the current Cleveland Session.

President Pepper announced that the terms of Dr. Jonathan C. Meakins and Dr. G. Gill Richards, as appointees from the American College of Physicians on the American Board of Internal Medicine, will expire June 30, 1940, and that appointments would be in order.

On motion by Dr. Robert A. Cooke, seconded by Dr. Roger I. Lee, and regularly carried, it was

RESOLVED, that the Board of Regents of the American College of Physicians shall reappoint as its representatives on the American Board of Internal Medicine for the term July 1, 1940 to June 30, 1943, Dr. Jonathan C. Meakins, of Montreal, and Dr. G. Gill Richards, of Salt Lake City.

After the reading of announcements concerning coming events, meetings, etc., in connection with the Twenty-fourth Annual Session, the meeting adjourned.

Attest: E. R. LOVELAND,  
*Executive Secretary*

# ANNALS OF INTERNAL MEDICINE

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